

A Neural Link to Understanding Rosacea: Focusing on Flushing Triggers

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Abstract

Facial erythema in rosacea can be triggered by events that do not normally cause sustained flushing. This review discusses why flushing was evolutionarily conserved, how facial blood flow increases, and how the process can go awry in rosacea. Known mechanisms of increased facial-skin blood flow associated with thermal/environmental, social/emotional, pharmaceutical/topicals, dietary, and physical-exercise trigger events are explored. Flushing triggers begin with neural (sympathetic, cranial nerve, axon reflex, or sensory afferent) responses inducing vasodilation (active vasodilation and/or reduced tonic vasoconstriction), fluid extravasation, and increased vascular volume. Local inflammatory mediators can augment responses, but it is neural responses that initiate the process. We theorize that mechanistically understanding erythema will allow rosacea to be better tolerated and controlled.

Introduction

Rosacea is a chronic skin disorder most commonly characterized by erythema and inflammatory lesions in the central face region, which affects many people worldwide, including an estimated 16 million people in the United States.¹ Disease classification often includes both subtypes and variants. Subtypes include erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea; variants include granulomatous and neurogenic rosacea.^{2,3} Regardless of classification or whether all patients can be adequately classified, most patients present at some point with induced or permanent facial flushing.⁴

Rosacea erythema, especially in the erythematotelangiectatic subtype, can change in intensity and is activated by trigger events. Erythema triggers vary among patients but can be grouped into categories related to thermal/environmental, social/emotional, pharmaceutical/topicals, dietary, and exercise (Table 1). In a recent National Rosacea Society survey, more than 50% of North American participants reported that hot weather and baths, sun and wind exposure, emotional stress, alcohol consumption, and exercise all trigger flushing and associated symptomatology.⁵ Besides acute erythema, these episodes can cause local inflammation, edema, and painful burning or stinging sensations. Chronic and repeated bouts of flushing and associated inflammation can induce structural changes in the vasculature (e.g., telangiectasias) and connective tissue, which add to disease signs and symptoms.

This review addresses what is known about the neural mechanisms underlying rosacea erythema trigger events. We discuss why flushing was evolutionarily conserved, how blood flow mechanistically increases in facial skin, and how it can go awry in disorders such as rosacea. A review with this particular focus, neural mechanisms of rosacea erythema triggers, has not been previously completed. Most mechanistic evaluations of rosacea have almost exclusively focused on the inflammatory aspects of the disease; while these

are important, it is the neural events (sympathetic, cranial nerve, axon reflex, and sensory afferent) that initiate the trigger. We refer the reader to a number of excellent reviews and source material that cover general information about rosacea, inflammatory and pathological changes associated with it, and its potential treatment.⁶⁻¹² Although etiology is unknown, current FDA-approved treatments in the United States include metronidazole, azelaic acid gel, and doxycycline,

which decrease inflammation associated with rosacea but do not generally improve the erythema. In contrast, neural (ganglionic, cholinergic, and α -adrenergic) antagonism strategies have been reported to reduce rosacea erythema.¹³⁻¹⁵ One interesting approach is the use of an α_2 -adrenergic agonist (brimonidine gel), which has recently been approved for treatment of rosacea erythema. This class of drug can directly cause some vasoconstriction via post-synaptic α_2 -

Table 1. Common rosacea triggers

Category	Examples	Stimulus/Mechanism
Thermal/Environmental	Sun	UV,* local and whole-body heating
	Hot weather	Local and whole-body heating
	Wind	Local heating and cooling, irritation, AVAs,** blood-pressure effect
	Hot bath, sauna	Local and whole-body heating
	Cold	Local and whole-body cooling, AVAs, blood-pressure effect
	Indoor heat	Local and whole-body heating
	Humidity	Whole-body heating
Social/Emotional	Embarrassment	Mental stress
	Psychological stress	Arousal, blood-pressure effect
	Anxiety	Mental stress, blood-pressure effect
	Sexual arousal	Arousal, whole-body heating
Pharmaceutical/Topical	Medications	Variable
	Skin-care products	Irritation, allergic
	Cosmetics	Irritation, allergic
	Alcohol	Direct effect, gustatory reflex
Dietary	Spicy food	Gustatory reflex
	Heated foods and beverages	Gustatory reflex
	Certain fruits and vegetables	Variable, unknown
	Dairy	Unknown
Exercise	Aerobic exercise	Whole-body heating
	Resistance exercise	Arousal, blood-pressure effect

* UV - ultraviolet

**AVA - arteriovenous anastomosis

adrenergic receptors on vascular smooth muscle but also reduces the release of neurotransmitters and modulators from these nerves via α_2 -adrenergic receptors located presynaptically on the adrenergic axon terminals. Our central theory is that if rosacea erythema triggers are mechanistically understood, better avoidance and treatment plans as well as prevention strategies for those more susceptible to this disease state can evolve.

Skin Blood Flow

To understand the erythema associated with rosacea, an understanding of the physiology of skin blood flow and its measurement is required. The advent of many noninvasive indices of skin blood flow (e.g., laser-Doppler flowmetry with both fixed probes and scanners, transcutaneous tissue oxygenation, in vivo video microscopy, photoplethysmography) has allowed measurements of indices of facial blood flow.¹⁶⁻¹⁸ The ease of use of these devices has allowed for increased utilization, but most dermatology-focused studies do not appropriately control for factors that affect skin blood flow independent of their treatment paradigm. For instance, not expressing laser-Doppler measures as cutaneous vascular conductance (flux/mean arterial blood pressure) is problematic because blood pressure increases flow independent of changes in luminal diameter of the blood vessel. This is especially important as arterial blood-pressure-to-flow relationships are dissimilar between glabrous and non-glabrous skin, and many trigger events are sympathetic nervous system stimulants that increase arterial blood pressure.^{19,20}

Also problematic is comparing groups and sites without skin-blood-flow standardization, as absolute values are uninterpretable unless density of blood vessels and other parameters are known – and in non-invasive studies, these are always unknown.

Combined with the neural and trigger foci discussed above, understanding the physiological mechanisms of skin blood flow, its assessment, and the control factors that govern responses and then applying these concepts to rosacea will provide new insights into this complex disease whose etiology is still for the most part unknown.

Facial Flushing

Facial flushing is common in many mammals for display (act of attracting attention or showing emotion) and heat dissipation. Humans have retained the capacity to increase blood flow to show emotion, such as flushing (blushing) in response to an embarrassing event or in response to frustrating circumstances. The questions of where, when, and why blushing occurs are difficult to answer. Charles Darwin said of blushing, "...a rather curious question why, in most cases the face, ears, and neck alone redden."²¹ He hypothesized that blushing could be due to generations of focus on the human face, possibly because of its role in communication. Highlighting this phenomenon, focused attention on a part of the

face during an embarrassing task corresponds to an increase in an index of skin blood flow in that area.²² It is thought that embarrassment, and in part blushing, may be a remnant of appeasement display that is observed in some social animals.²³ In sum, flushing should be considered a normal physiological response that can aid in providing social cues and conveying emotion.

Facial flushing can also participate to a minor extent in heat dissipation. Humans can lose heat from the face and head but primarily rely on hairy skin of the rest of the body for heat dissipation. Both in glabrous skin (e.g., nose, ears) and other facial areas (e.g., forehead, cheek), blood flow can increase during times in which heat dissipation is necessary, but because of hairy skin's sheer surface area and large blood flow capacity (up to 8 L/min), there is a much greater potential to offload heat in hairy skin.²⁴⁻²⁶ In addition to differences in skin blood flow, there are also neural, anatomical, and functional differences between the types of skin (Table 2). Notably, there is vasomotor cranial-nerve involvement in facial mucosa and skin but not in peripheral glabrous and hairy skin.²⁷ Thus, for primary heat dissipation, humans rely not on facial flushing but on blood-flow changes in non-facial hairy skin.

If facial flushing is normal during embarrassment and heat-stress conditions, what constitutes a flushing disorder? There are a number of factors and disorders that can cause flushing.²⁸ The differential diagnosis of the rosacea patient who presents with flushing, sensitive skin and facial edema can be difficult.⁷ Rosacea's most visible sign, facial erythema that fluctuates in intensity with trigger events, is defined by its pathophysiology,

which includes neurovascular dysregulation and inflammation.¹² The subsequent sections of the review discuss the neural origins of these erythema triggers based on patient-frequency data and trigger categorization.

Rosacea Erythema Trigger Mechanisms

In rosacea, no erythema trigger is universal.⁵ In the current review, we refer to triggers as having major (>50% of survey respondents), moderate (25%-50%), and minor (<25%) incidence rates and will discuss only the major and moderate triggers.⁵ Rosacea erythema triggers can be roughly categorized into five groups (Table 1), with varied mechanisms of induction of facial flushing and associated symptomatology. The study of facial blood flow is made more difficult because certain mechanistic pharmacological procedures (e.g., intradermal microdialysis) cannot be completed in the human face for safety and ethical reasons. Glabrous skin also suffers transcutaneous drug delivery difficulties due to its thick epidermal layer. Thus, the majority of mechanistic in vivo studies are completed in the hairy skin of the forearm, calf, or thigh. Nonetheless, a discussion of erythema triggers as they relate to forearm, leg, and palm skin with the inclusion of face skin when available provides a framework to investigate flushing mechanisms in the face and in individuals with rosacea.

Thermal/Environmental

Whole-body heat stress is a major rosacea flushing trigger that induces a number of physiological changes to improve the body's ability to dissipate

Table 2. Characteristic differences between types of human skin

Type	Neural	Anatomical	Functional
Hairy	Adrenergic vasoconstrictor	Surface capillary loops	Heat dissipation
	Cholinergic-related vasodilator		
	Cholinergic sudomotor		Tissue insulation
	Adrenergic pilomotor		
Glabrous	Adrenergic vasoconstrictor	Surface capillary loops	Grip and dexterity
	Cholinergic sudomotor	Arteriovenous anastomoses (AVAs)	
Facial	Cranial nerves	Surface capillary loops	Display
	Adrenergic vasoconstrictor		
	Cholinergic-related vasodilator?	Arteriovenous anastomoses (AVAs)	Heat dissipation
	Cholinergic sudomotor		
Adrenergic pilomotor?			

heat.⁵ Notably, there are sympathetically mediated increases in heart rate and cardiac output; vasoconstriction of renal, splanchnic, and skeletal muscle vasculatures; and vasodilation of the skin to facilitate environmental heat transfer.²⁹ Glabrous, hairy, and facial skin are under tonic sympathetic vasoconstrictor tone, as evidenced by the release of vasoconstriction with ganglionic blockade or presynaptic release inhibitor and the existence of basal skin sympathetic nerve activity.^{20,30-37} All skin types appear to utilize a release of vasoconstrictor tone to increase skin blood flow during a whole-body heat stress. Peripheral hairy but not glabrous skin also employs a cholinergic-related active vasodilator system.^{32,38} Although peripheral hairy skin has functional β -adrenergic receptors, it appears that facial skin may be more reliant on these receptors during stress.³⁹⁻⁴¹ It is unknown if facial skin also relies on the same cholinergic-related active vasodilator mechanism that peripheral hairy skin does. Schwab and colleagues identified marked vasodilation in affected areas in all subtypes of rosacea but did not resolve the vasoactive substance(s) or the origin(s) thereof.⁴² Additional research is needed to determine whether changes in facial vasodilator mechanisms are implicated in rosacea during whole-body heating.

Local skin heating, also a major rosacea flushing trigger, induces vasodilation that is sympathetic-independent but requires adrenergic innervation for complete expression.^{5,43-45} This vasodilation occurs in a biphasic manner in peripheral hairy skin, where the initial vasodilation is primarily due to an axon reflex and the later vasodilation to a nitric-oxide-mediated response.⁴⁶ Local-heating-induced vasodilation occurs in facial skin but is not consistently observed in peripheral glabrous skin.⁴⁷ Facial (i.e., forehead and cheek) axon reflex responses follow hairy skin's biphasic vasodilation pattern but are unique in that standard topical anesthetic protocols are not successful in blunting the initial, axon-reflex-associated vasodilation.⁴⁷ Guzman-Sanchez identified increased local heat sensitivities in both erythematotelangiectatic and papulopustular rosacea.⁴⁸ This result is consistent with an upregulation of the heat-activated transient receptor potential vanilloid-1 (TRPV1) channel in erythematotelangiectatic rosacea and greater nerve-fiber densities in all subtypes of rosacea.^{42,49} Thus, it is possible that the face has a greater axon-reflex component compared to peripheral hairy and glabrous skin and that this response is heightened in rosacea-affected areas.⁵⁰

Ultraviolet (UV) exposure associated with sunlight is another major rosacea flushing trigger.⁵ This stimulus is likely multifactorial, involving whole-body and local heating mechanisms resulting from UV-induced heat gain in addition to the unique activity of UV radiation itself. It is unclear whether UVA (320-400) or UVB (290-320 nm) triggers symptoms. Although UVA is the dominant component of solar radiation, it requires greater energy to induce a minimal erythema dose.⁵¹ DNA is a chromophore, a UV-photon absorber, and in response to UVB-photon bombardment it creates a number of

proinflammatory photoproducts, such as DNA-repair enzymes, TNF- α , and other cytokines.^{52,53} Photoproducts associated with tryptophan, another chromophore, increase expression of COX-2 and thereby catalyze erythema, producing PGE₂ and PGE₃ during UVB exposure.⁵² UVA travels deeper into the skin and thus affects the dermal layer to a greater extent. UVA damage is perfusion- and O₂-dependent, which heavily implicates a reactive oxygen species (ROS) mechanism.⁵⁴ Finally, both UVB and UVA exposures upregulate both vascular endothelial growth factor and toll-like receptor (TLR) pathways, which could mediate angiogenesis and cytokine synthesis and secretion.^{55,56} This latter effect may sensitize the skin for subsequent UV-exposure responses. Whether these UV processes are altered in facial compared to peripheral hairy and glabrous skin or in rosacea, however, remains to be determined.

Whole-body cold stress, a moderate rosacea flushing trigger, induces a number of physiological changes to increase tissue insulation and decrease environmental heat loss.⁵ Passive cold stress does not change cardiac output but causes systemic vasoconstriction, thereby increasing vascular resistance and arterial blood pressure.^{57,58} Despite this pressure increase, both peripheral hairy and glabrous skin undergo pronounced decreases in cutaneous vascular conductance during whole-body cooling. Peripheral hairy skin normally remains vasoconstricted throughout a cold stress; however, skin with arteriovenous anastomoses (e.g., glabrous skin) can oscillate between constricted and relaxed states. This cyclical response has been termed the "hunting reaction," as it is thought to increase flow to aid in dexterity and prevent tissue freezing without losing extraordinary amounts of heat.²⁶ Thus, in response to whole-body cooling, arteriovenous anastomosis-rich areas such as the nose, ears, and lips can increase blood flow, although responses in other areas of the face are less clear. Facial skin's absolute vasoconstriction in response to cooling may also be blunted or absent because many facial locations such as the forehead do not appear to contain a high density of cutaneous vasoconstrictor nerves.³⁶ Thus, it is possible that there are regional arteriovenous anastomosis responses and less opposition to the increases in arterial blood pressure. This could be a mechanism to decrease blood flow in some facial skin while increasing skin blood flow to other facial areas during whole-body cooling. It is possible that the arteriovenous anastomosis response is altered in patients with rosacea, possibly due to changes in the neural control of this response.

Local cooling can also be a moderate rosacea flushing trigger.⁵ In peripheral hairy skin, locally applied cold produces biphasic vasomotor responses. An initial vasoconstriction is followed by a transient vasodilation and then a prolonged vasoconstriction.⁴⁶ The mechanisms by which local cooling causes these vascular changes, with the exception of α_{2C} -adrenergic receptor translocation, are unclear but likely involve local sensory afferents. Under thermoneutral

conditions, α_{2C} -adrenergic receptors are located in the Golgi apparatus membrane. Then, with mitochondrial ROS stimulation, such as during local cooling, the Golgi apparatus migrates to the cell surface and fuses with the existing cell membrane. This increases α_{2} -adrenergic receptor density, which allows for greater vasoconstrictor per quanta of norepinephrine released from sympathetic nerves. To our knowledge, the local cooling response in facial skin has not been described. Facial skin could be different in that it has a higher density of sensory afferents, which could lead to an augmented counteracting of vasodilation depending on pain and other sensory afferent vasoactive releases.^{42,59,60} Whether sensory afferent or other neural control of facial blood flow during local cold stress is altered in rosacea needs further clarification.

Wind is listed as a distinct and major rosacea flushing trigger, but the specific temperature is not accounted for in most surveys.⁵ Cold-wind responses may be related to local and whole-body cooling responses. Wind causes direct skin-temperature changes via convective cooling and may also cause irritation and thus induce sensory afferent responses similar to local cooling. Wind may also dry superficial skin layers, leading to a disruption of the skin barrier. If a hot or cold wind causes a great enough skin-temperature change, it may locally exacerbate or attenuate skin-blood-flow responses per change in internal temperature.⁶¹ Another possible cold-wind outcome, if applied directly to the face, is a "diving" reflex response that results in decreased heart rate and increased arterial blood pressure.⁶² Experimental "diving" reflex procedures decrease skin sympathetic nerve activity to peripheral glabrous and hairy skin; this reduction in vasoconstriction coupled with increased arterial pressure could lead to increased skin blood flow.^{63,64} Little is known about wind or convective cooling, outside the "diving" reflex, in facial skin. Similarly, possible changes in rosacea have yet to be determined.

Social/Emotional

Emotional stress and anxiety are both major rosacea flushing triggers.⁵ Embarrassment is often not precisely delineated in rosacea surveys, but it is a very common cause of increased blood flow in facial skin (see Facial Flushing section) and is likely related to emotional stress. The precise mechanisms of emotional-stress-induced flushing are poorly understood. One theory relates to a catecholamine surge (likely neural due to timing) and associated β -adrenergic vasodilation. Peripheral hairy skin also possesses β -adrenergic receptors but not in a great enough density to induce erythema in these areas.³⁹ Sudomotor activity to peripheral glabrous skin increases during embarrassment, but less is known about the response in skin blood flow. Validating these observations, mental stress increases peripheral glabrous and hairy skin sympathetic nerve activity.^{65,66} Mental stress also increases supraorbital-skin sympathetic nerve activity, and this increase is accentuated in those with erythematotelangiectatic rosacea.⁶⁷

However, Drummond and Su did not observe differences in an index of forehead-skin blood flow in those with rosacea while performing embarrassing tasks; this is despite those with rosacea reporting greater embarrassment and intensity of blushing compared to controls.⁶⁸ There may be differences in neural responses to mental stress vs. embarrassing tasks, but it is possible that rosacea symptoms are due in part to supraorbital-nerve overactivity or altered issues of perception.

Pharmaceutical/Topical

Certain cosmetics, skin care products, and topical medications applied to the face are classified as moderate rosacea flushing triggers.⁵ Defining this category's mechanism of action is difficult because of the plethora of potential skin care products, but it most likely results from either skin irritation or an allergic reaction to the product. Sensory afferent nerves sense skin irritation, while the wheal and flair response of a typical allergic reaction involves an axon reflex. It is also possible that these irritations could not only increase skin blood flow but also compromise the skin barrier, leading to increased transepithelial water loss and inflammation. This disrupted and inflamed facial skin barrier in rosacea appears to be involved in the increased susceptibility to contact dermatitis and a more vigorous response to cutaneous irritation.⁶⁹ Issues associated with rosacea-induced disruption of the facial skin barrier and how this relates to topicals require further research.

Dietary

Consumption of alcohol (ethanol) is a major rosacea flushing trigger.⁵ Alcohol is associated with small amounts of cutaneous vasodilation, especially in the face and periphery.⁷⁰ The vasodilation effect is thought to be due to the direct effect of ethanol on vascular smooth muscle.⁷¹ Facial flushing is pronounced in individuals with aldehyde dehydrogenase inactivation due to a point mutation, but this mutation likely does not account for alcohol's potential trigger effect in most individuals with rosacea.⁷² It is possible that either individuals with rosacea are more sensitive to cutaneous vasodilation or that the ethanol induces a gustatory flushing response similar to that of hot drinks or spicy foods.

Hot drinks are classified as a moderate rosacea flushing trigger.⁵ Originally it was thought that the trigger was related to the caffeine in coffee or tea, but more recent investigations identified an oral-cavity heat effect.⁷³ Wilkin suggested that heat draining from the oral cavity into the jugular vein heats carotid-artery blood via a countercurrent system.⁷³ While some heat exchange occurs between vessels, it is more likely that the very warm temperatures (60 °C) cause a reflex vasodilation as occurs in other gustatory reflexes.²⁷ This level of heat stimulates TRPV1 receptors on warm sensory afferents, which could lead to a cranial-nerve reflex response. It is unclear to what extent individuals with rosacea have abnormal gustatory reflexes.

Spicy-food consumption is also classified as a moderate rosacea flushing trigger and may utilize a TRPV1-channel mechanism similar to that of the oral sensation of heat.⁵ The classic response to spicy products is capsaicin-mediated, although other chemicals that are perceived as spicy could also be involved. Kashima and Hayashi observed increases in an index of skin blood flow throughout the face with oral capsaicin administration.⁷⁴ Capsaicin-induced vasodilation occurs via TRPV1-receptor stimulation, which causes flushing through the gustatory parasympathetic vasodilator pathway.³⁰ This reflex response via a cranial nerve is different from acute or chronic topical capsaicin administration.^{75,76} As described previously, the increase in TRPV1-receptor gene expression in erythematotelangiectatic rosacea could provide a potential mechanism whereby rosacea may result in hyperactive gustatory-reflex responses.⁴⁹

Physical Exercise

Physical exercise is another major rosacea flushing trigger.⁵ On surveys, this concept is often referred to as “carrying and lifting” (resistive exercise) or “walking, running, bicycling” (aerobic exercise). Physical stress increases arousal, which increases skin sympathetic-nerve activity to peripheral glabrous and hairy skin as well as facial areas independent of changes in metabolism.^{36,65,77-80} The level of effort, but not the amount of muscle mass engaged in the effort, determines the increase in peripheral skin sympathetic-nerve activity in response to resistive exercise.^{79,81,82} Exercise task visualization and direct motor-cortex stimulation increase peripheral skin sympathetic-nerve activity, indicating that feedback from the exercising muscle is not needed to increase sympathetic activity.^{83,84} Individuals with rosacea have augmented supraorbital skin sympathetic-nerve activity to resistive exercise.⁶⁷ Thus, it is possible that this sympathetic-outflow increase is part of the reason for erythema in these patients. The responses of peripheral skin sympathetic-nerve activity in rosacea are unknown, and thus it is unknown if the augmented responses are limited to the face or reflect a global response.

Aerobic exercise causes an internally generated heat stress. Thus, similar to whole-body heat stress, widespread sympathetically mediated increases in skin blood flow conduct heat to the skin for dissipation. A few caveats associated with aerobic exercise-induced heat stress vs. environmental or passive heat stress: 1) There is an anticipatory or feed-forward aspect of exercise, where peripheral skin sympathetic-nerve activity increases prior to the generation and sensation of heat stress; and 2) internally generated heat (exercise heat stress) can occur more rapidly than passive heat stress.^{84,85} Further research is needed to determine whether changes in sympathetic or other neural responses during aerobic exercise are implicated in rosacea.

Perspectives and Conclusions

Flushing is a normal facial physiologic process that becomes hyperactive in individuals with

rosacea, often resulting in exaggerated responses; over time, persistent erythema, inflammation, and telangiectasia can develop. Highlighting these blood-vessel changes, using capillaroscopy, Rosina and colleagues described increases in vessel diameters, vessel tortuosity, and telangiectasia in rosacea-affected areas.⁸⁶ Flushing triggers are numerous and individualized but can be grouped into thermal/environmental, social/emotional, pharmaceutical/topical, dietary, and exercise-related items. These erythema triggers begin with neural events such as sympathetic nervous system, cranial nerve, axon reflex, or sensory afferent responses. The nervous system, in addition to affecting inflammation, both directly and indirectly controls blood-vessel diameter and thus blood flow. The facial vasculature is innervated by post-synaptic sympathetic fibers and cranial nerves and is affected by axon reflexes, sensory nerves, and locally released paracrine substances. Because ganglionic blockade, intradermal botulinum toxin A, and adrenergic blockade have been reported to reduce flushing, potential roles for the sympathetic nervous system are implicated.^{15,30,31,87-89} Individuals with rosacea appear to have overactive supraorbital sympathetic responses to mental and physical stress, which further implicates this mechanism. Cranial nerves participate in cutaneous vasodilation via such responses as axon and gustatory reflexes.²⁷ Individuals with rosacea may also have altered facial axon reflexes, which could contribute to these augmented reflex responses.⁵⁰ When activated, sensory nerves release local vasodilator agents (e.g., CGRP and ATP) and can stimulate keratinocytes, sweat glands, and mast cells, releasing substances such as prostaglandins, bradykinin, and histamine. Prostaglandins, bradykinin, and histamine are potent vasodilators, increase vascular permeability, and produce edema. Although still unknown, it is possible that individuals with rosacea release more of these or are sensitized to inflammatory substances. The current understanding of the pathophysiology of rosacea, including the inflammatory cascade involving TLR2 and serine protease KLK5 expression and abnormal forms of cathelicidin peptides (LL-37 and FA-29), is described in detail elsewhere.^{9,42,90} While this inflammatory cascade is important, the neural events initiate these processes. Over time, these erythema triggers can also lead to structural and functional adaptations that characterize the disease. Understanding these neural links and physiological responses to erythema triggers may help to focus future rosacea treatments on mechanistically stopping disease progression earlier and potentially in a more individualized manner by targeting mechanisms of each patient's specific triggers, allowing rosacea to be better tolerated and controlled.

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