REVIEW ARTICLE

Adult skin acute stress responses to short-term environmental and internal aggression from exposome factors

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Abstract

Exposome factors that lead to stressed skin can be defined as any disturbance to homeostasis from environmental (meteorological factors, solar radiation, pollution or tobacco smoke) and/or internal exposure (unhealthy diet, hormonal variations, lack of sleep, psychosocial stress). The clinical and biological impact of chronic exposome effects on skin functions has been extensively reviewed, whereas there is a paucity of information on the impact of short-term acute exposure. Acute stress, which would typically last minutes to hours (and generally no more than a week), provokes a transient but robust neuroendocrine-immune and tissue remodelling response in the skin and can alter the skin barrier. Firstly, we provide an overview of the biological effects of various acute stressors on six key skin functions, namely the skin physical barrier, pigmentation, defences (antioxidant, immune cell-mediated, microbial and microbiome maintenance), structure (extracellular matrix and appendages), neuroendocrine and thermoregulation functions. Secondly, we describe the biological and clinical effects on adult skin from individual exposome factors that elicit an acute stress response and their consequences in skin health maintenance. Clinical manifestations of acutely stressed skin may include dry skin that might accentuate fine lines, oily skin, sensitive skin, pruritus, erythema, pale skin, sweating, oedema and flares of inflammatory skin conditions such as acne, rosacea, atopic dermatitis, pigmentation disorders and skin superinfection such as viral reactivation. Acute stresses can also induce scalp sensitivity, telogen effluvium and worsen alopecia.

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Introduction

The skin is one of the largest and most diverse barrier organs of the human body with the epidermis constituting the first line of defence against environmental stressors, e.g. meteorological factors (extreme heat, cold, humidity), solar radiation including ultraviolet radiation (UVR), pollution or tobacco smoke. At the same time, the skin is also affected by internal stressors, e.g. an unhealthy diet, hormonal variations, lack of sleep and psychosocial stress. Together, these challenges to the skin homeostasis constitute the skin exposome, a term which refers to the totality of exposures to such non-genetic factors encountered by an individual over their lifetime.[1,2] The clinical and biological impact of chronic exposome aggressions on skin functions has been extensively reviewed,[1–6] whereas there is a paucity of information on the immediate effects of short-term acute exposure, which is the aim of this review.

Exposome factors that lead to acutely stressed skin can be defined as any acute disturbance to homeostasis after environmental and/or internal exposure. Acute stress, which would typically last minutes to hours (and generally no more than a week in humans), thereby provokes a transient but robust response. This response from the key skin functions, including the skin barrier, pigmentation, defences (biochemical and immune/cellular), structure (extracellular matrix and skin appendages), neuroendocrine and thermoregulation functions, is aimed at protection or rapid elimination of the disturbance and return to homeostasis. In the present review, focussing on adult skin, we describe individual exposome factors that elicit an acute stress response and their corresponding impact on the key skin functions.

Skin functions affected by acute stress responses

Acute environmental and internal stressors can affect several skin functions. An overview of six key skin functions and their role in acute stress responses is shown in Fig. 1. Upon exposure to acute stress, these skin functions are coordinated by a transient activation of multiple biological mechanisms, some of which will be specific to different stressors, whereas others will be common to all of the stressors we review, as discussed below.

1 The epidermal physical barrier is the main mechanical defence against extrinsic factors including toxic damage, allergens and microbes, while it is also responsible for maintaining stratum corneum hydration by preventing unregulated trans-epidermal water loss (TEWL).[7–9] The initial step in the repair response to an acute stressor is rapid secretion (within minutes) of the contents of the lamellar bodies from the outer stratum granulosum cells.[10] Rapidly acting skin barrier disruption recovery mechanisms include greater epidermal cell proliferation and lipogenesis, and increased adhesion molecule expression.[11]

2 Skin pigmentation protects the basal keratinocytes from UV-induced DNA damage.[12] The UVB-induced DNA damage in keratinocytes promotes the activation of the p53 protein that binds the pro-opiomelanocortin (POMC)

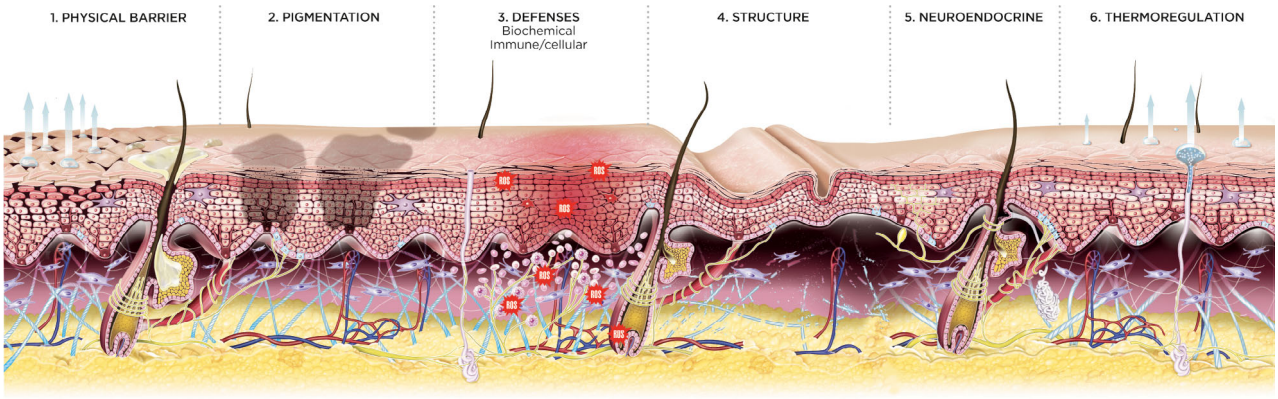

Figure 1 Skin functions affected by acute stressors. 1. The skin physical barrier or stratum corneum, consisting of differentiated keratinocytes (corneocytes) encased in lipid lamellae and tight junctions, is important for lipid synthesis, skin hydration and desquamation that play a role in skin dryness, tightness and skin sensitivity. 2. Melanocytes and interacting keratinocytes have a key role in skin pigmentation. 3. Skin biochemical defences have a role in antioxidant response, osmolyte strategy, DNA repair and pain, while immune/cellular defences have a role in skin immunity, including inflammation (e.g. in exacerbation of psoriasis, atopic dermatitis, seborrhoeic dermatitis, acne), Langerhans cells, decreased immunity with risk of superinfection and alteration of the skin microbiome (e.g. reactivation of viral infections under psychological stress and UV radiation). 4. The skin structure including the extracellular matrix and adnexa (hair follicles, sebaceous glands, sweat glands) plays a role in hypersudation and development of telogen effluvium. 5. Skin neuroendocrine delivery by vasculature and innervation involves local production of neurotransmitters, neurotrophins, neuropeptides, hormones with a role in the neurogenic inflammation (e.g. pain and pruritus), triggering the HPA axis, increased endocrine, vegetative and neuropeptidergic excitability levels. 6. The thermoregulation function involving blood vessels and fat has a role in vasoconstriction and flushes (e.g. rosacea)

promoter and ultimately induces the secretion of alpha-melanocyte-stimulating hormone (α-MSH) that stimulates the MC1R melanocortin receptor on the melanocytes and activates the melanogenesis.[13] High energy visible light directly triggers pigmentation by stimulating a specific receptor called Opsin 3 at the melanocyte membrane.[14]

3 The skin´s defence mechanisms are aimed at damage control. The biochemical defences to acute stress include antioxidant response, DNA repair and cellular osmolyte strategies.[15] An increase in reactive oxygen species (ROS) can induce the expression of matrix metalloproteinases (MMP) and promote the degradation of collagen, which can be attenuated by antioxidants.

Immune cell-mediated defences are coordinated with the neuroendocrine response.[16,17] Acute stress primarily includes the innate immune system of the skin, involving antimicrobial peptides, Langerhans cells (LC), mast cells, monocytes and granulocytes as well as the epidermal keratinocytes and structural cells present deeper in the dermis, such as endothelial cells and fibroblasts.[18] Among them, the LC in the epidermis coordinate the role of stressor recognition. Acute stress additionally triggers the recruitment of natural killer (NK) cells, phagocytic cells, basophils and neutrophils into the dermis by the release of pro-inflammatory cytokines. Immune activating damage-associated molecular patterns (DAMPs), e.g. alarmins, activate Toll-like receptor (TLR) signalling,[19] and increased production of pro-inflammatory cytokines such as interleukin-1 (IL-1) β and tumour necrosis factor (TNF)-α.[7] Mediators of subsequent acquired, adaptive innate immunity are pro-inflammatory cytokines of T helper cell type 1 (Th1).

Skin microbiota play an integral role in the maturation and homeostatic regulation of keratinocytes and host immune networks. The skin microbiome and skin-resident memory T cells may abrogate the immunosuppressive response following acute stress.[20,21]

4 Defensive structures of the skin, especially the extracellular matrix, densely innervated and vascularized dermis and subcutis (nerve fibres), and skin appendages (hair follicles, sebaceous glands, sweat glands), provide the second line of defence from foreign intruders as well as internal damage. Sebaceous and eccrine glands secrete increased amounts of sebum and sweat in response to acute stress leading to moist, cool and slippery skin.

5 A heightened neuroendocrine-immune response to acute stressors (e.g. heat, trauma, infestations) clinically manifests as erythema, oedema and hypersensitive responses such as pruritus or pain. The skin is one of the most densely innervated organs of the body.[22–24] Acute stress activates the sympathetic axis of the autonomous nervous system (SA), which reacts very quickly and leads to a transient release of adrenaline from the adrenals and a local release of noradrenaline from peripheral adrenergic nerve fibres. The SA triggers activation of the endocrine hypothalamus–pituitary–adrenal axis (HPA), resulting in a transient release of cortisol from the adrenals into the blood stream, while the release of corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol from skin cells form a local equivalent of the central HPA.[25] Skin homeostasis is maintained by the additional activation of the cholinergic axis of the autonomic nervous system (CA). In addition, neuropeptides are either released from sensory nerve fibres or produced locally. Substance P (SP) and calcitonin gene related peptide (CGRP) are the main neuropeptides that modulate immediate-type skin hypersensitivity reactions. This neuronal neuropeptidergic axis (NNA) response to acute stress regulates multiple tissue remodelling and inflammatory processes, some of which are acutely inflammatory such as mast cell activation and subsequent neurogenic inflammation,[18,26,27] while others down-regulate inflammatory processes. Acute stressors can induce the neurotrophic factors such as artemin, nerve growth factor (NGF) or brain derived neurotrophic factor (BDNF) which contribute to hyper-innervation, allokinesis and inflammation via, e.g. the aryl hydrocarbon receptor (AhR) and neurotrophin receptors. Acute stress triggers peripheral vasoconstriction by activating transient receptor potential (TRP) channels associated with neurogenic inflammation causing pale skin as well as rapid mobilization of immune cell trafficking into the skin.[28,29] It also leads to the release of melatonin, which contributes to immunomodulation, thermoregulation and tumour control.

6 Blood vessels and fat have a role in sympathetically mediated vasoconstriction and flushing under acute stress, causing a rapid drop in skin temperature.[30]

Biological and clinical effects of distinct skin stressors

Acute solar radiation

Acute solar radiation not only stimulates pigmentation and induces DNA damage but also promotes oxidative stress, inflammation (e.g. sunburn, photosensitivity, photoallergy, flares of photodermatoses), decreased immunity against microbial challenges (e.g. herpes labialis photo-immunosuppression with viral reactivation), Koebner phenomenon after acute sunburn, barrier function alteration, osmolyte strategy and microbiome alteration.

The damage response effect of UVR on the skin immune system has recently been reviewed.[19] The first-line defence of UV-induced oxidative stress is the acute activation of the oxidative pentose phosphate pathway to increase NADPH production, which is essential to prevent oxidative damage.[31] Exposure to

UVB (290–315 nm) or UVA (340–400 nm) radiation significantly stimulates osmolyte uptake to protect cells against oxidative stress.[15,32] UVR can compromise epidermal barrier function causing skin dryness and enabling the penetration of bacteria and allergens.[33] Immediate short-term response to UVR-induced damage is mediated by the innate immune system of the skin and involves epidermal keratinocytes, melanocytes, LC, dermal endothelial cells, fibroblasts, mast cells, dendritic cells (DC), resident lymphocytes and neural elements, with subsequent recruitment of myeloid cell types, such as neutrophils, monocytes and macrophages.[19] In a mouse model, a single high dose of UV was shown to produce a deep inflammatory state characterized by the production of pro-inflammatory cytokines and chemokines.[34] Sunburn from acute UVB exposure is characterized by epidermal cell necrosis, decreased antigen presentation and acute inflammation. UVR induces the release of DAMPs that activate TLR signalling.[19] Acute UVR rapidly activates skin-resident T cells through mechanisms involving the release of ATP from keratinocytes to limit DNA damage in keratinocytes. UVR induces the epidermal recruitment of DC that compensate for the depletion of LC in human skin.[35] The effector functions of T cells depend on the activation state of LC by UVR. In response to UVB exposure, Treg cells are induced to maintain skin homeostasis and participate in epithelial stem cell differentiation of hair follicle cycles.[36–38] The skin microbiome may abrogate the immunosuppressive response following acute UV exposure.[21] Alternatively, direct UV-induced DNA and membrane damage to the microbiome may result in pathogen associated molecular patterns that interfere with UV-induced immune suppression.[20] In addition, acute UV exposure causing flushes and vasodilatation can decrease blood pressure.[39]

Beneficial effects of acute UV exposure include synthesis of vitamin D, release of opioid factors and decrease in pain.[40–42]

Acute solar radiation exposure leads to tanning and endothelial cells and fibroblasts activate melanocytes to induce pigmentation, which may cause postinflammatory hyperpigmentation (PIHP), especially for darker phototypes, or trigger photodermatoses, such as polymorphous light eruption. Melanocytes can protect from UV damage and contribute to the regulation of acute bursts of oxidative stress in the skin.[43]

UVR, especially UVB, stimulates cutaneous neurogenic mediators that affect the central HPA and increase inflammation.[44,45] CRH is upregulated in human sebocytes and keratinocytes in vitro by UV.[46] In mice, cutaneous exposure to UVB rapidly stimulated systemic CRH, ACTH, β-endorphin and corticosterone production accompanied by rapid immunosuppressive effects in splenocytes.[47] The rapid induction of immune suppression appears to be independent of the HPA axis (immunostimulation) and may be via direct neuronal activation.[47] In mice, pro-inflammatory neuropeptides are released from skin nerve fibres in response to UV exposure.[48]

UV radiation and heat (as well as cold, stress, spicy food and microbes) are trigger factors of rosacea that may modulate TLR signalling, induce ROS and enhance antimicrobial peptide and neuropeptide production.[49,50]

The hypodermis contains a network of blood vessels that connects the local effects of UVR exposure to systemic immunosuppression effects and fever, if large body surfaces are exposed.[51–53] Acute UV exposure may inhibit the function of antigen-presenting cells, induce T cells with suppressor activity and induce the release of immunosuppressive cytokines and the latter phenomenon is mainly responsible for systemic immunosuppression.[53] Acute UV total body exposure, psychosocial stress and hormonal variations can all cause a comparable mast cell activation and release of IL-6 cytokine release with systemic effects.[54]

Acute pollution

Airborne pollutants induce cutaneous oxidative stress and have been shown to damage skin barrier integrity by altering TEWL, inflammatory signalling, stratum corneum pH and the skin microbiome. Short-term pollutant exposure has been linked to xerosis, pruritus and exacerbation of atopic dermatitis symptoms.[55]

After 4 h exposure to volatile organic compounds (VOC), epidermal barrier damage was observed within 48 h in sensitized subjects with atopic eczema.[56]

In an ex vivo skin model, diesel exhaust particles increased skin pigmentation, expression of pigmentation related genes and induced expression of MMP and pro-inflammatory cytokines and these hyperpigmentation and inflammaging effects were reduced by application of an antioxidant mixture.[57]

Among air pollutants, ozone is one of the most toxic due to its unstable structure and is able to initiate oxidative reactions and activate inflammatory response, leading to the onset of several skin conditions.[58,59] In vivo and in vitro studies have shown that short-term acute exposure to ozone impacts skin defences by production of ROS, biomolecule oxidation (lipid peroxidation and protein carbonylation), depletion of cellular antioxidant defences, cell stress and cytotoxicity.[1,60–62] Ozone can induce inflammasome activation in a redox dependent manner in a mouse model, which may play a role in pollution-induced inflammatory skin conditions.[63,64] When human forearm skin was exposed to ozone for 2 h, vitamin E decreased 70% with a concomitant increase in lipid hydroperoxides and a 50% decrease in the residual skin microflora in the superficial stratum corneum without producing a visible clinical response.[65] Ozone reacts with skin lipids and squalene peroxidation by-products cause cytotoxic, pro-inflammatory, immunological events and may lead to irritation, comedones and inflammatory acne.[66] Toxic effects of ozone are mediated through free radical reactions, leading to lipid peroxidation. In a clinical study in which skin was exposed ozone (0.8 ppm three times daily for 5 days), skin biopsies showed

significant increases in α-β unsaturated aldehyde 4-hydroxynonenal and 8-iso-prostaglandin-F(2a) protein adducts, while topical application of vitamin C appeared to prevent this oxidative modification of proteins.[60]

Short-term exposure to NO_2 or VOC caused significantly increased TEWL in both healthy individuals and those with atopic dermatitis.[56,67] A time-series study showed increased outpatient visits for acne vulgaris in Beijing when there was high air pollution (particulate matter $[PM]_{10}$, $PM_{2.5}$, SO_2, NO_2).[68] Various organic components of pollutants interact with the AhR in keratinocytes to elicit an epidermal hyper-innervation via induction of the neurotrophic factor artemin that causes nerve growth hypersensitivity, pruritus and an atopic dermatitis pathology.[69] Furthermore, retrospective time-series studies on large populations of patients showed a relationship between a rising incidence of emergency department visits for urticaria and atopic dermatitis with an increased ambient level of ozone,[70] PM and SO_2.[71] An effect of air pollution and meteorological factors (temperature and humidity) on the number of hospital outpatient visits for atopic dermatitis was also observed.[72]

Combined acute challenges of UV and pollution

UV may act synergistically with particulate matter, causing an acute skin response with increased tissue peroxidation and decreased cutaneous α-tocopherol causing additive oxidative stress in the stratum corneum.[73,74] Ozone, PM and UV radiation synergistically increased oxidative stress and oxinflammation changes in human skin explants.[59,64]

Abrupt meteorological changes (humidity and temperature)

Dry environmental conditions can markedly enhance epidermal structure and function.[75] In hairless mice exposed 1–2 weeks in a dry environment (<10% relative humidity [RH]), TEWL was significantly lower, while epidermal hyperplasia, lamellar body secretory system and lamellar membranes were all increased, and barrier recovery was accelerated when compared to a humid environment (>80% RH).[75] A clinical study on dry facial skin found a higher dryness score with low temperatures, high wind speed and low humidity, and 15 min of exposure to cold and dry air led to a reduction in skin hydration.[76] These data suggest that lower temperatures lead to a decrease in skin hydration and TEWL and that this effect is stronger at low RH. Furthermore, a study to evaluate the effect of RH on the facial skin of Japanese volunteers observed lower skin conductance, lower elasticity and increased mean area of fine wrinkles after 30 min at low humidity (40% RH) compared to higher humidity (70% RH, all $P < 0.05$).[77]

In an ex vivo study, stratum corneum water content increased 50% in vivo and pliability of skin when the temperature was raised from 20 to 35°C at RH below 60%.[78]

Low humidity and low temperatures decrease skin barrier function and increase susceptibility towards mechanical stress, while the skin also becomes more reactive towards skin irritants and allergens as pro-inflammatory cytokines and cortisol are released by keratinocytes, and the number of dermal mast cells increases.[79] Cold and dry weather appear to increase the prevalence and risk of flares in patients with atopic dermatitis.[67,79] However, cold alone for short periods of time (six cycles of 4°C for 90 s) did not affect TEWL or skin irritation.[80]

Acute exposure to heat can cause *erythema ab igne*, a reticulated, hyperpigmentation of the skin.[81]

Acute psychosocial stress

While chronic stress generally leads to pathogenic immune responses,[82,83] acute stress may induce a defensive response coordinated by a momentary and transient activation of the multiple stress response systems including activation of pro-inflammatory mediators with immune-enhancing effects. Acute psychosocial stress induces activation of the SA, HPA and NNA, triggering vasoconstriction, neurogenic inflammation and pro-inflammatory mediator release and subsequently the anti-inflammatory CA in an attempt to maintain homeostasis.[16,30,82] Inflammasome activation, upregulation of NK cell activity and upregulated release of Th1 cytokines via peripheral SA activation and via sensory nerves can protect against acute infectious agents as well as skin cancers;[83] this may contribute to better control of viral infections.[84] In mice, short-term restrain stress before UV exposure also led to greater cutaneous T-cell attracting chemokine, IFN-γ gene expression and higher infiltrating T cell numbers.[85] Of note, physical pain (3-min cold pressor pain stimulus) can cause acute psychological stress. Subjects who reported higher pain showed faster skin barrier recovery, and greater increase in norepinephrine (but not cortisol for HPA activation) was also associated with faster recovery and mediated the impact of pain on skin barrier repair.[86,87] The immune-enhancing effect of acute stress is hence homeostatic. However, if the stress is intense or buffering resources low, the heightened neuroendocrine-immune response becomes toxic and clinically manifests as erythematous rashes, oedema, pruritus or intense pain. Low neuropeptide oxytocin levels and high pro-inflammatory cytokines are associated with both stress and pain, which may explain how psychological distress affects pain at skin level in patients with traumatic stress symptoms from burn wounds.[88]

Acute psychosocial stress may negatively affect skin structure by inhibiting hair growth under the influence of the HPA via cortisol release in addition to a SP-mast cell pathway.[18,89] Increased oxidative stress and redox impairment due to psychosocial stress could affect levels of pro-inflammatory cytokines, as reported after short-term (minutes) stress when students were preparing for an examination.[90]

Autoimmune diseases, such as alopecia areata and vitiligo, may be triggered by acute stress with altered innate and adaptive responses and increased oxidative stress.[91] Acute emotional stress may precipitate alopecia areata by activation of overexpressed type 2β CRH receptors around the hair follicles leading to intense local inflammation.[92]

Acute psychosocial stress may reactivate skin infectious diseases (herpes zoster, herpes labialis, herpes genitalis) via SA activation leading to increased vulnerability to infectious diseases due to skin barrier impairment and immune defence, as well as modified microbiota.[93]

Acute emotional distress could lead to increased levels of glucocorticoids (GC) and androgens inducing increased sebum production in acne as well as increasing production and release of CRH from dermal nerves and sebocytes.[94–96] Increases in proinflammatory cytokines, SP and lipids due to stress may also contribute to aggravation of acne.[97–99] Accordingly, in 22 subjects with acne vulgaris, severity was aggravated by emotional stress (evaluated 3 days before and 7 days after an examination).[100]

Acute psychosocial stress, sleep deprivation and nutritional factors all have an effect on epidermal barrier integrity, host immune response and neurogenic factors, which can result in worsening of seborrhoeic dermatitis.[101] In psoriasis, stress promotes acute inflammation, driven by TNF-α and epithelial hyperplasia through the SA and NNA.[102] Adults with atopic dermatitis show blunted HPA responsiveness to acute stress but hyperreactivity of the SA,[103] and an association between onset or flare of atopic dermatitis lesions and psychosocial stress has been observed.[104]

If acute psychosocial stress persists and becomes chronic, it can cause severe and long-lasting health problems in the case of chronification, as reviewed elsewhere.[16,105] Briefly, this stimulates a persistent increase in endogenous GCs that compromises permeability barrier homeostasis, stratum corneum cohesion, wound healing and epidermal innate immunity in normal skin. Stress and skin barrier injury then lead to better penetration of pathogenic microbes and increase vulnerability to cutaneous infectious diseases, such as superficial viral infections, mycosis and impetigo. This maladaptive state of the brain–skin connection may underlie inflammatory skin diseases caused or aggravated by stress, e.g. acne, rosacea, atopic dermatitis and psoriasis.[49,100,102]

Acute sleep deprivation

Sleep loss results in an elevation of cortisol levels the next evening.[106] Acute total sleep deprivation significantly increases stress-related hormones (with dysregulation of the HPA and activation of the NNA), making it difficult to differentiate between effects of stress and acute sleep deprivation.[107]

Acute stress and one night of sleep deprivation may cause skin barrier impairment[7] that could aggravate skin dryness, intensify itch and worsen atopic dermatitis.[108–110]

Sleep deprivation may increase oxidative stress and release of ROS.[111] Circadian imbalance could elevate levels of several potential somnogenic cytokines, including TNF-α, interleukin (IL)-10 and C-reactive protein, that could be related to cortisol dysregulation due to poor sleep.[107] An impact on the immune system from lack of sleep could manifest as autoimmune diseases.[112] In Caucasian women (56 women aged 25–35 and 55 women aged 55–65 years old), fatigue from a working day induced mild changes in facial signs (infraorbicular dark circles) and slightly accentuated wrinkles.[113] In another study, in Chinese women (aged 20–40 years old), fatigue induced dull and tired-looking skin and these signs were more pronounced in the older women aged 31–40 years old.[114]

Acute sleep deprivation induced changes in thermoregulation in rats resulting in a decreased peripherical surface temperature due to SA activation during acute stress.[115] However, two nights of sleep deprivation with or without energy restriction did not impair the thermal response to cold in human subjects.[116,117]

Acute nutrition/alcohol intake

Certain foods and dietary patterns can trigger acute changes that lead to visible skin effects. For example, consumption of alcohol, hot beverages, spicy food, capsaicin and cinnamaldehyde activate TRP channels, contributing to facial erythema and rosacea.[118–120] Changes in sebaceous gland composition have been documented after 5 to 7 days of fasting. In one trial, human subjects showed a marked change in forehead skin lipids, with suppression of sebaceous gland synthesis of all lipids (apart from squalene).[121]

Other acute effects include biochemical and cellular changes, hormonal changes, changes in the gut microbiome and inflammatory cytokine effects. These acute changes may all impact skin disease, either directly or indirectly, even if clinical lesions will not necessarily be acutely visible. For example, large shifts in the gut microbiome have been documented to occur within 24 h, with potential implications on skin innate immunity and inflammation.[122]

In acne, three major dietary components have been studied for their clinical impacts. These include hyperglycaemic carbohydrates, dairy products and certain patterns of fat consumption, including increases in saturated and trans fats and fewer ω-3 polyunsaturated fatty acids (PUFAs).[123] In the cascade of events, cytokine production is acutely triggered by diet and the cellular changes occur acutely (inflammation, keratinocyte proliferation, hyperseborrhoea), as do hormonal effects, although clinically apparent acne lesions may not be acutely visible. Diet-mediated changes include an increase in sebum production as well as a change in sebum composition.[124] This promotes the overgrowth of *Cutibacterium acnes* and increases levels of free palmitate. Free palmitate stimulates an inflammatory cascade, with resulting increases in IL-1β, Th17 differentiation and IL-17-mediated keratinocyte proliferation.[123,125] This

Table 1 A summary table of the main biological mechanisms and clinical effects of acute exposure to exposome factors

Acute stress	Skin function affected	Main biological mechanisms	Clinical manifestations
Solar radiation	Barrier	TEWL	Dryness
	Pigmentation	Melanogenesis	PIHP, tanning, melasma exacerbation, dark spots
	Defences	Oxidative stress,[31] DNA damage, inflammation,[19] decrease in epidermal Langerhans cells,[35] Treg expansion,[36,37] microbiome alteration,[21] photoimmunosuppression[19]	Sunburn, photosensitivity, photoallergy, actinic keratoses, viral reactivation, herpes labialis. Improvement of some dermatoses (psoriasis, atopic dermatitis), Koebner phenomenon, photodermatoses (e.g. polymorphous light eruption)
	Neuroendocrinology	Neurogenic inflammation,[44,45] upregulation of CRH,[46,47] vitamin D synthesis, opioid release,[42] decreased blood pressure[39]	Pruritus, hypersensitivity, atopic dermatitis, rosacea
	Thermoregulation function and systemic effect	Vasodilatation[49,50]	Fever, erythema, rosacea flushes
	Skin structure	Hyaluronic acid degradation from epidermis and dermis extracellular matrix degradation via oxidative stress	Dryness, wrinkles, skin laxity
Pollution	Barrier	Change in sebum, squalene peroxidation[58]	Dryness, skin sensitivity Flares of acne, atopic dermatitis
	Pigmentation	Pigmentation[57]	Dark spots
	Defences	Oxidative stress,[60,61] microbiome alteration,[65] pro-inflammatory immune response	Flares of acne, atopic dermatitis
	Neuroendocrinology	Neurotrophic factor artemin[69]	Pruritus, flares of atopic dermatitis
Pollution and ultraviolet radiation	Defences	Oxidative stress[74], pigmentation, oxinflammation[64]	Photoaging, dark spots and wrinkles
Meteorological changes	Barrier	TEWL,[75,78] sebum production	Dryness, oily skin and scalp, pruritus, flares/ improvement of atopic dermatitis, psoriasis
	Structure	Hypersudation	Sweat
	Defences	Inflammation[67]	Skin sensitivity, flares of atopic dermatitis, rosacea
Psychosocial stress	Barrier	TEWL, tight junction dysfunction	Dryness, transgression of microbes, toxins, allergens
	Structure		Piloerection, sweating, hair loss by anagen termination and telogen effluvium, alopecia
	Defences	Oxidative stress, inflammation[102], immune suppression	Flares of acne, rosacea, psoriasis, alopecia areata, vitiligo, seborrhoeic dermatitis, atopic dermatitis, skin superinfection, viral reactivation
	Neuroendocrinology	Neurogenic inflammation, hyper-innervation,[87,88,90] upregulation of CRH[94–96]	Erythema, oedema, pruritus, pain
	Thermoregulation	Vasodilation, vasoconstriction	Pale skin, hypothermia, redness
Sleep deprivation	Barrier	TEWL[7]	Dryness, dullness
	Defences	Oxidative stress,[111] inflammation[107]	Pruritus, flares of psoriasis, atopic dermatitis, seborrhoeic dermatitis, acne, skin superinfection, viral reactivation
Nutrition	Barrier	Lipid/ sebum production[121,124]	Dry skin, oily skin
	Defences	Antioxidant, inflammation,[123] allergic reactions,[130] microbiome[122]	Acne, atopic dermatitis, systemic contact dermatitis
	Neuroendocrinology		Flushing, rosacea exacerbations
Hormonal variations	Skin barrier		Oily skin, dry skin
	Structure	Hypersudation	Telogen effluvium, androgenic alopecia
	Defences	Oxidative stress, melatonin (antioxidant), oxytocin[140], inflammation[136,138]	Acne, atopic dermatitis, aphtous ulcers
	Neuroendocrinology	Stimulation of the HPA,[142,143] GC,[144] modulation of skin neuropeptides[145]	Progesterone dermatitis

Table 1 *Continued*

Acute stress	Skin function affected	Main biological mechanisms	Clinical manifestations
Medications and procedures	Skin barrier		Irritation, dryness and erythema
	Defences	Inflammation, antimicrobial response,[152,153] changes in microbiome	Acne, superinfection, viral reactivation
Mask use, disinfectants, frequent washing	Barrier and defence	Skin temperature, sebum, TEWL[158]	Dryness, pruritus, skin sensitivity, erythema, acne and rosacea flares

CA, cholinergic axis; CRH, corticotrophin-releasing hormone; HPA, hypothalamus–pituitary–adrenal axis; PIHP, postinflammatory hyperpigmentation; TEWL, trans-epidermal water loss;

cascade contributes to the visible sebofollicular inflammation in acne vulgaris.[123]

Hormonal changes have also been documented. In human subjects, a 7-day controlled feeding trial reported short-term effects of a low glycaemic load diet, suggesting that increases in dietary glycaemic load may increase the biological activity of sex hormones and IGF-1.[126] Another randomized controlled crossover trial documented a significant increase in acne lesions (14.8 lesions) in a group consuming chocolate versus a jelly bean group (−0.7 lesions, $P < 0.0001$), when evaluated 48 h later.[127] The authors noted that dairy was a confounding factor, but hypothesized that chocolate components modulating cytokine production led to inflammation.[127]

Food allergies are another example of acute effects and may worsen atopic dermatitis [128–130] due to immediate-type IgE-mediated hypersensitivity (rarely in adults; reactions occur within hours), systemic contact dermatitis (reactions typically occur 24–48 h later)[131] or delayed eczematous reactions (24–48 h later).[132]

Acute hormonal variations

The skin is itself an endocrine organ, and all its components are constantly regulated by hormones.[133] The main hormones that affect the skin include sex hormones (oestrogens, progesterone, androgens), neuroendocrine hormones (GC, CRH, melatonin) and others (thyroid, growth hormones).[133–138]

Acute postpartum hormonal variations may cause telogen effluvium.[139] Skin and hair follicles express melatonin that is a powerful antioxidant to combat ROS from acute stress responses. Oxytocin is released during labour and is a neuroendocrine mediator in human skin homoeostasis and modulates key processes which are dysregulated in atopic dermatitis such as proliferation, inflammation and oxidative stress responses.[140]

Progesterone dermatitis hypersensitivity symptoms are associated with the progesterone surge during the luteal phase of the menstrual cycle or after exposure to exogenous progestins.[141] Hormonal variations can induce stimulation of the HPA,[142,143] GC[144] and modulation of skin neuropeptides.[145] Premenstrual variations in hormones have been reported to cause acne flares,[94] aphthous ulcers[146] and exacerbation of atopic dermatitis symptoms.[147]

Medications and procedures

Procedures such as peels, botulinum neurotoxin, soft tissue fillers, lasers and microdermabrasion may cause skin barrier disruption, inflammation, PIHP and skin superinfection. Topical retinoids can cause retinoid irritation dermatitis, skin irritation, dryness and erythema due to skin barrier alteration, especially in the first days/weeks.[148] Topical and systemic retinoids have been reported to alter sebum quantity and quality and affect the facial skin microbiome, e.g. by reducing or eradicating the anaerobe *Cutibacterium acnes* which is involved in the complex pathogenesis of acne vulgaris.[149–153] Antibiotic use for acne and acute bacterial skin infections may alter the skin microbiome.[154,155]

Acute stress challenges to skin during the COVID-19 pandemic

The use of face masks, gloves and repeated hand sanitization has been associated with high rates of adverse skin reactions among healthcare professionals with reports of acute and chronic dermatitis, secondary infection and aggravation of underlying skin diseases such as acne, seasonal facial dermatitis, seborrhoeic dermatitis and rosacea.[156,157] In a cross-sectional study in 34 healthcare workers, TEWL, temperature and erythema were all significantly increased after 2 h of glove and mask use, indicating impaired epidermal barrier function.[158] Possible mechanisms of aggravation of acne by mask wearing include rupture of comedones induced by pressure and friction, occlusion of pilosebaceous units, microcirculation dysfunction due to long-term pressure, and bacterial proliferation due to higher temperature and humid environment caused by expired air and perspiration.[159]

How to prevent and improve stressed skin

Understanding the pathogenesis of a maladaptive stress response is essential for the development of therapeutic strategies to improve skin health during acute exposome stress exposure.

The main biological effects of these acute stressors on skin include skin barrier alteration, subclinical microinflammation, inflammation, immunosuppression, DNA damage, melanogenesis, alteration of sebum and sweat production. The main clinical consequences include skin dryness or oiliness, dullness, redness, skin sensitivity, pruritus, sweating, flares of inflammatory skin conditions, skin superinfections such as viral reactivations, skin hyperpigmentation, as well as scalp sensitivity and hair loss. Repeated acute stressors may lead to enduring clinical effects contributing to skin ageing or skin cancers.

Global prevention measures include:

1 Avoidance of sunburn by adequate sun protection, e.g. sunscreen use, sun avoidance, protective clothing.
2 Adopting a healthy lifestyle, e.g. sleeping well, eating a well-balanced diet, acquiring stress management skills, the use of psychosocial interventions.
3 Reinforcing the skin physical barrier and defences against exposome factors with, e.g. antioxidants, antipollution products, probiotics, moisturizers, unsaturated fatty acids.

Conclusions

Cutaneous perturbations created by acute exposures induce responses to protect the organism and re-establish homeostasis. The main biological effects and resulting clinical manifestations of these acute exposures to individual external and internal exposome factors are summarized in Table 1. In adult skin, any acute stress effects should be contextualized against the background of chronic exposome exposures, especially in the case of chronic diseases, as well as the genome of the individual. Further research is required to elucidate individual effects from multiple stressors and may lead to a greater understanding of clinical presentations of skin disease at different times.

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