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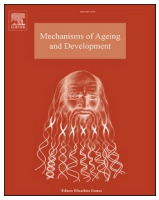

Exploring the interplay between stress mediators and skin microbiota in shaping age-related hallmarks: A review

Marco Duarte [a,1], Sílvia Santos Pedrosa [a,2], P. Raaj Khusial [b], Ana Raquel Madureira [a,*,3]

[a] Universidade Católica Portuguesa, CBQF - Centro de Biotecnologia e Química Fina – Laboratório Associado, Escola Superior de Biotecnologia, Rua Diogo Botelho 1327, Porto 4169-005, Portugal
[b] Amyris Biotech INC, 5885 Hollis St Ste 100, Emeryville, CA 94608-2405, USA

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ABSTRACT

Psychological stress is a major contributing factor to several health problems (e.g., depression, cardiovascular disease). Around 35 % of the world's population suffers from it, including younger generations. Physiologically, stress manifests through neuroendocrine pathways (Hypothalamic-Pituitary-Adrenal (HPA) axis and Sympathetic-Adrenal-Medullary (SAM) system) which culminate in the production of stress mediators like cortisol, epinephrine and norepinephrine. Stress and its mediators have been associated to body aging, through molecular mechanisms such as telomere attrition, mitochondrial dysfunction, cellular senescence, chronic inflammation, and dysbiosis, among others. Regarding its impact in the skin, stress impacts its structural integrity and physiological function. Despite this review focusing on several hallmarks of aging, emphasis was placed on skin microbiota dysbiosis. In this line, several studies, comprising different age groups, demographic contexts and body sites, have reported skin microbiota alterations associated with aging, and some effects of stress mediators on skin microbiota have also been reviewed in this paper. From a different perspective, since it is not a "traditional" stress mediator, oxytocin, a cortisol antagonist, has been related to glucorticoids inhibition and to display positive effects on cellular aging. This hormone dysregulation has been associated to psychological issues such as depression, whereas its upregulation has been linked to positive social interaction.

1. Introduction

Skin suffers several changes, overtime, gradually losing the capacity to adjust to the environment and it ages. Skin aging is a process, originated by decreased structural integrity and physiological function, which is brought on by both intrinsic (chronological) and extrinsic (environmental) factors (Castro et al., 2023). Psychological stress is an intrinsic factor that contributes to premature skin aging.

Around the world, stress is recognized as a leading cause of long-term sickness, resulting in millions of lost workdays (e.g., Am. Psychol. Assoc. 2019, UK Health Saf. Executive 2019) (O'Connor et al., 2021). The repeated activation of stress responses and the consequent overexposure to cortisol and other stress hormones put us at high risk for a variety of health issues, such as anxiety, depression, heart disease, stroke, and sleep problems, among others (APS, 2023). According to *The American Institute of Stress*, stress affects about 35 % of the world's population, including younger generations, who are nowadays experiencing elevated stress. It acts through neuroendocrine pathways, especially by stimulating the hypothalamic-pituitary-adrenal (HPA) axis, and ends in the adrenal cortex by the release of glucocorticoids, especially cortisol, the so-called stress hormone (AIS, n.d.; O'Connor et al., 2021). Besides the HPA axis and cortisol, catecholamines (epinephrine and norepinephrine) via adrenergic stimulation represent an important stress response mechanism (Radek, 2010). Psychological stress has been shown to have a harmful effect on physical well-being, including skin health (Lee et al., 2020). Skin is the largest human organ (including the hypodermis), with approximately 2 m^2. It carries out several important functions such as protection against trauma, solar (ultra-violet, UV) radiation, toxins and infections, preservation of water and electrolytes, thermoregulation, and water, vitamin D (produced by the skin after

* Corresponding author.
E-mail address: rmadureira@ucp.pt (A.R. Madureira).
[1] https://orcid.org/0009-0003-0878-8752
[2] https://orcid.org/0000-0002-2055-8031
[3] https://orcid.org/0000-0001-6596-1927

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stimulation with UVB radiation (Slominski et al., 2018a)) and fat storage. Additionally, skin is important in blood pressure regulation and excretory physiological function (Castro et al., 2023; Gilaberte et al., 2016; Walters and Roberts, 2002).

In addition to stress, the connection between skin microbiota and skin aging, often overlooked, has been documented not as direct cause but rather as an outcome. The skin microbiota represents the microbial community composed by millions of bacteria, fungi, and viruses, which inhabit our skin. When healthy, the skin microbiota and its host are in balance, maintaining skin homeostasis, which benefits human health by preventing the colonization of pathogenic microorganisms and assisting in the upkeep of the immune system (Carvalho et al., 2023; Fricker et al., 2019; Lee et al., 2019; Naik et al., 2012). There are two categories of skin microbes: resident and transient. Among the most studied components, which are bacteria, the four main phyla are Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes, while the most prevalent genera are *Cutibacterium*, *Staphylococcus* and *Corynebacterium* (Carvalho et al., 2023; Filaire et al., 2019; O'Sullivan et al., 2019; Yamazaki et al., 2017). Concerning the fungal community, *Malassezia* species are the most prevalent, accounting for 80 % of fungi (Carvalho et al., 2023).

A search was conducted in the PubMed database to determine the number of papers published with the following entry words: (1) "(psychological stress) AND (skin aging)"; (2) "(skin aging) AND ((microbiota) OR (microbiome))"; (3) "((psychological stress) AND (skin aging)) AND ((microbiota) OR (microbiome))". The search results are presented in Fig. 1. From this data, it is possible to understand that there is a growing interest in these topics. Nonetheless, considering the 3 topics together (search 3), only one study was found, indicating that this is a scientific field that needs exploring, with lots of knowledge gaps and future development opportunities. The year of 2023 was not included.

2. Neuroendocrinology of the skin: 'cutaneous HPA axis' and impact of UV radiation

Besides the aforementioned functions, the skin also presents several neuroendocrine capabilities. For instance, skin acts as a target for neuroendocrine signals, where both resident and transient skin cells express receptors for neuropeptides, hormones, neurohormones and neurotransmitters (e.g., corticotropin-releasing hormone (CRH), melanocortin, neurotrophins, vitamin D, glucocorticoids, cholinergic, adrenergic, and serotonin receptors, among others) similar to those expressed in the central neuroendocrine systems. Additionally, skin also functions as a source of hormones and neurotransmitters (produced by epidermal and dermal cells), and of neuropeptides (released by cutaneous nerve endings or directly by the skin), which exert well-known systemic effects (Slominski and Wortsman, 2000; Slominski et al., 2022). In this regard, it is well established that skin possess a neuroendocrine system equivalent to the HPA axis, which is commonly known as "skin pro-opiomelanocortin (POMC) signaling system". This system relies on the fact that skin cells are capable of producing POMC peptides (e.g., adrenocorticotropic hormone (ACTH), α-melanocyte stimulating hormone (α-MSH), *β*-endorphin, and *β*-lipotropic hormone (*β*-LPH) (Day, 2009)) and to simultaneously express functional receptors in a cell type-, species-, and context-dependent manner (Slominski et al., 2013a). Nonetheless, this system is conceivable due to interactions between the epidermis, dermis, and hypodermis, which, because of the absence of considerable spatial separation, allow the 'cutaneous HPA axis' elements to operate in a coordinated or independent manner in para-, auto-, and intracrine ways, resulting in a variety of phenotypic outcomes and potential diseases. The key element is the activation of the CRHR1 (Corticotropin Releasing Hormone Receptor 1) by either CRH or urocortin, followed by a signaling cascade that leads to the generation and release of POMC peptides, including ACTH, with downstream effects such as corticosteroidogenesis: CRH → CRHR1 → POMC → ACTH → COR (e.g., cortisol) (Slominski et al., 2022).

This way, other crucial skin hormones include catechols and biogenic amines (catecholamines, serotonin, and N-acetyl-serotonin, histamine) (Gillbro et al., 2004; Grando et al., 2006; Schallreuter et al., 1992; Slominski et al., 2005a; Slominski et al., 2012a; Slominski et al., 2020; Theoharides and Cochrane, 2004), acetylcholine (Grando, 2006; Grando et al., 1993), melatonin and its metabolites (Fischer et al., 2008a; Fischer et al., 2008b; Slominski et al., 2005b; Slominski et al., 2008; Slominski et al., 2012a), CRH and related urocortins (Krause et al., 2007; O'Kane et al., 2006; Paus et al., 2006; Slominski, 2003; Slominski

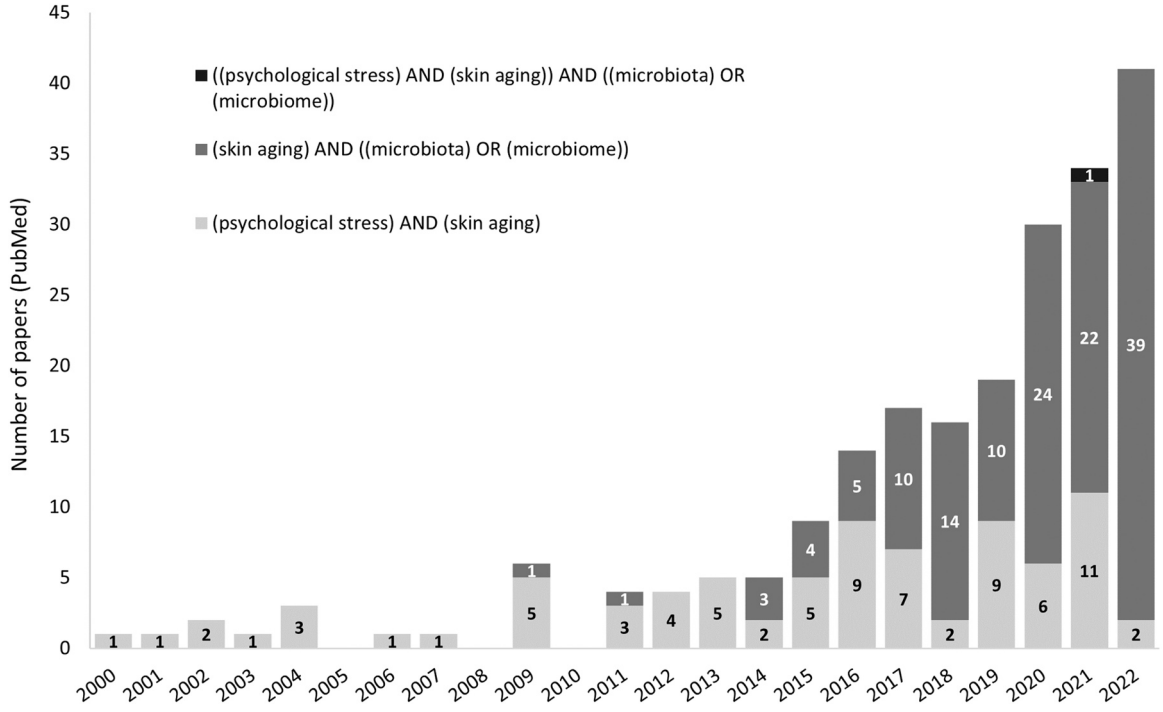

Fig. 1. Number of papers in PubMed database related to psychological stress, skin aging, and microbiota, according to the indicated entry words.

et al., 2001; Slominski et al., 2006a), corticosteroids and their precursor molecules (Slominski et al., 2004; Slominski et al., 2007), among others.

There are several factors that regulate the cutaneous neuroendocrine system, from which UV radiation (especially UVA and UVB) stands out as the most prominent one (Slominski and Wortsman, 2000). Importantly, UV radiation is the principal cause of extrinsic skin aging, also known as photoaging. Photoaging is responsible for over 80 % of facial aging, and photoaged skin is featured by deep wrinkling, loss of elasticity, dryness, and laxity (Gu et al., 2020; Kammeyer and Luiten, 2015; Silva et al., 2017). UV radiation causes cumulative skin degradation, which is influenced by the frequency, duration, and intensity of the exposure, as well as the natural skin pigmentation (Kammeyer and Luiten, 2015). Similarly to what happens with intrinsic aging, photoaging also results in decreased number and physiological function of keratinocytes and fibroblasts, leading to impaired barrier function and degraded ECM (e.g., decreased collagen and elastin) (Gu et al., 2020). All these factors add to intrinsic aging, and often are more severe (Gu et al., 2020). Interestingly, and despite being an external aggressor (e.g., cancer, aging, autoimmune responses), UV radiation may trigger neuroendocrine mechanisms that regulate local and systemic homeostasis (Slominski et al., 2018a).

For instance, using animal models, the Hiramoto group showed that UVB-induced α-MSH stimulates cutaneous melanocytes (Hiramoto et al., 2003; Hiramoto et al., 2013), while UVA downregulates cutaneous Langerhans cells (Hiramoto, 2009). Moreover, the authors showed deterioration of ulcerative colitis by UVB and its improvement by UVA (Hiramoto et al., 2016), and improvement of atopic dermatitis by UVA (Hiramoto et al., 2018). UVA was also shown to stimulate β-endorphin in the skin (Skobowiat et al., 2011) and colon with concomitant increases of methionine-enkephalin and attenuation of colonic carcinogenesis (Hiramoto et al., 2017), and modulation of mucosal intestinal functions (Yamate et al., 2011). Additionally, UVB can also stimulate β-endorphin in the skin (Skobowiat and Slominski, 2015; Skobowiat et al., 2011; Skobowiat et al., 2013), plasma (Fell et al., 2014; Skobowiat and Slominski, 2015; Skobowiat and Slominski, 2016; Skobowiat et al., 2017), and brain (Skobowiat and Slominski, 2015; Skobowiat and Slominski, 2016; Skobowiat et al., 2017), which may be linked to the "UVB addiction" phenomenon (Fell et al., 2014; Kourosh et al., 2010; Nolan et al., 2009) as well as to nociceptive and other behavioural effects (Fell et al., 2014; Skobowiat and Slominski, 2016; Slominski et al., 2012b). Moreover, UVB was reported to induce CRH gene expression and peptide production in epidermal melanocytes, keratinocytes (Skobowiat et al., 2011; Slominski et al., 1996; Zbytek et al., 2006a), and dermal fibroblasts (Slominski et al., 2006a).

Furthermore, 1,25$(OH)_2$D3 (active form of vitamin D_3), and non-calcemic vitamin D analogs (Slominski et al., 2005c; Slominski et al., 2015; Zmijewski et al., 2011) have been shown to induce the expression of CRH, urocortins, POMC, and their respective receptors in human skin (Wierzbicka et al., 2016). Also, it has been hypothesized that sunlight deprivation and lower levels of vitamin D_3 derivatives may raise the risk of breast, colon, and prostate cancers (Studzinski and Moore, 1995). Moreover, recent evidence suggests that vitamin D plays a role in upregulating tryptophan hydroxylase type 2, leading to increased brain serotonin and complex behavioral effects (Kaneko et al., 2015; Patrick and Ames, 2014; Patrick and Ames, 2015). Thus, vitamin D metabolites could indirectly contribute to UVB-induced behavioural effect or even impact the HPA, CRH, and POMC signaling systems at the peripheral or central levels (Slominski et al., 2018a).

In addition, it has been suggested that UV radiation is capable of regulating internal organs through brain or spinal cord reflexes (Slominski and Wortsman, 2000). In fact, a study showed that UVB stimulation of back skin resulted in inhibition of the Agouti-Related Protein (*AgRP*) in a time- and dose-dependent manner, and the authors suggested that UVB may be linked with the central regulation of body metabolism and feeding behaviour (Skobowiat and Slominski, 2016;).

In this regard, emerging evidence shows that UV radiation therapy has potential for treating drug addiction and mood disorders due to its opioidogenic effects (Fell et al., 2014; Skobowiat and Slominski, 2015; Skobowiat and Slominski, 2016; Slominski et al., 2011; Slominski et al., 2012b), as well as regulating body metabolism, food intake, and appetite through effects on POMC, CRH, and *AgRP* signaling (Skobowiat and Slominski, 2016; Slominski, 2015).

In sum, skin not only is affected by systemic molecules (hormones, neuropeptides, etc) such as cortisol or epinephrine, which will be our main focus throughout the paper, but it also has the capacity to sense foreign stimuli (intrinsic ones, e.g., brain hormones, or extrinsic ones, e.g., UV radiation) and to respond to them, releasing several compounds that may exert local or systemic impact on skin/body homeostasis. This is very interesting because it becomes clear the existence of a brain-skin axis that functions bidirectionally, one having the capacity to affect the other.

That said, in the next sections, we will address the impact of psychological stress (an intrinsic aging factor) and its mediators on the skin aging process.

3. Stress mediators and their impact on skin

When we experience psychological stress, two major systems are activated. The sympathetic-adrenal-medullary (SAM) system is the first and simplest to activate. The second is the HPA axis (O'Connor et al., 2021). Both these systems function through the action of several hormones, which in this paper we call "stress hormones" or "stress mediators". Importantly, these hormones have some effects on the skin, which we will discuss in the following subsections.

3.1. Hypothalamic-Pituitary-Adrenal axis

In response to psychological stress, the hypothalamus releases CRH, a peptide hormone. Once released, it travels via the bloodstream to the pituitary gland, where it promotes the release of ACTH. Following that, ACTH travels through the circulatory system to the adrenal cortex, where it promotes the synthesis of the glucocorticoid cortisol, the so-called stress hormone (AIS, n.d.; O'Connor et al., 2021). Besides this hormone-cascade in response to stress, cortisol is also produced in hair follicles, melanocytes, and fibroblasts (Chen and Lyga, 2014), and is reported to have classical anti-inflammatory activity (Polsky et al., 2022). It decreases type I collagen and hyaluronic acid production, provokes skin atrophy and thinning, and alterations in keratinocytes and fibroblasts morphology and number, increasing the risk of infection and impaired wound healing (Choo et al., 2023). Besides cortisol, also CRH and ACTH, and their receptors are expressed in skin cells (Kim et al., 2013; Slominski et al., 2013b). Under stress, CRH is synthesized by epidermal and hair follicle keratinocytes, melanocytes, sebocytes, and mast cells (Kono et al., 2001; Slominski et al., 2001). The role of CRH in the skin is multifaceted and cell-type specific. For instance, in epidermal keratinocytes, CRH reduces proliferation by arresting cells during the G0/1 cycle and causes differentiation via calcium influx and AP-1 transcription pathway (Zbytek et al., 2005; Zbytek and Slominski, 2005). Furthermore, CRH works as a growth factor in dermal fibroblasts and melanocytes, inducing proliferation, and preventing their apoptosis when stressed by starvation (Slominski et al., 2006b). Also, it increases degranulation and enhances vascular permeability in mast cells, indicating pro-inflammatory activity (Theoharides et al., 1998). Additionally, CRH promoted the production of pro-inflammatory cytokine IL-6 in keratinocytes (Zbytek et al., 2002). On the other hand, it suppressed NF-kB signaling in melanocytes, potentially to self-inhibit the inflammatory response (Zbytek et al., 2006b). Moreover, CRH increased lipid synthesis in a human sebocyte model by up-regulating critical lipogenesis enzymes (Zouboulis et al., 2002). Also, patients with psoriasis and atopic dermatitis, skin conditions known to worsen with stress, had higher serum levels of CRH (Vasiadi et al.; 2012). In response to CRH signaling, human melanocytes and dermal fibroblasts produce ACTH

and corticosterone, via the cAMP pathway (Slominski et al., 2005d; Slominski et al., 2005e). ACTH has been found in keratinocytes, Langerhan cells, monocytes, and macrophages (Slominski et al., 2000). It promotes the synthesis of IL-18 in keratinocytes. IL-18 is a pro-inflammatory cytokine that increases T-cell activity and stimulates the production of T helper type 2 (Th2) cytokines (Park et al., 2007). Since CRH suppresses IL-18 in keratinocytes (Park et al., 2005), this cytokine may be involved in the negative feedback loop that governs HPA axis activity (Chen and Lyga, 2014). Also, ACTH increases melanocyte proliferation and melanogenesis the same way that α-MSH does (Suzuki et al., 1996; Dissanayake and Mason, 1998). In addition, ACTH can stimulate sebocyte differentiation by acting on the MC5R receptor (Zhang et al., 2006). Moreover, endogenous ACTH was shown to increase hair growth, in a mouse model (Paus et al., 1994).

3.2. Sympathetic-adrenal-medullary system

When in stress (e.g., threatened or frightened), the brain immediately activates the ANS (Autonomic Nervous System), inducing norepinephrine production in the adrenal glands, which in turn stimulates the internal organs. This is the fundamental sympathetic response of the ANS to a danger. Simultaneously, the adrenal medulla produces epinephrine, which is rapidly carried via the bloodstream to prepare the body further to respond. Within seconds, adrenaline (epinephrine) and noradrenaline (norepinephrine) have the entire body on alert, the so-called "fight-or-flight" response (increased heart rate and breathing, blood vessels constriction except in the muscles, pupil dilatation, decreased digestive system activity). (Chen and Lyga, 2014; O'Connor et al., 2021). Catecholamines are also produced in the skin and have an impact on it. In this regard, the authors feel it is important to give credit to Karin Uta Schallreuter, current Clinical Director of the Institute for Pigmentary Disorders (Ernst Moritz Arndt University of Greifswald), and colleagues for the significant advances in this area, with emphasis on the synthesis and degradation of catecholamines in the epidermis, and their respective effects, for example, at the level of keratinocyte differentiation, melanin production, and the impact on skin conditions such as vitiligo (Gillbro et al., 2004; Salzer and Schallreuter, 1995; Schallreuter, 1997; Schallreuter et al., 1992; Schallreuter et al., 1995; Schallreuter et al., 1999). For instance, keratinocytes produce epinephrine, and the adrenergic receptors are expressed in both epidermal keratinocytes and melanocytes (Grando et al., 2006). After epinephrine activates the β2-adrenoceptor in keratinocytes, it causes a significant rise in cAMP, which elevates calcium concentration via protein kinase C activation (Koizumi et al., 1997; Schallreuter et al., 1992). Since calcium levels can influence epidermal proliferation and differentiation, epinephrine may impact epidermal health (Chen and Lyga, 2014). Additionally, epinephrine synthesized by surrounding keratinocytes can enhance melanogenesis in melanocytes (Gillbro et al., 2004), and it is reported to affect fibroblasts functions such as migration and collagen production, both crucial for wound healing (Romana-Souza et al., 2011).

3.3. Other stress mediators

Apart from the two systems we previously discussed, there are other less relevant stress hormones, which may impact the skin's health. Since the skin is densely innervated, peripheral nerves can influence skin health via secreted substances such as neuropeptides (e.g., substance P) and neurotrophins (e.g., nerve growth factor (NGF)) (Botchkarev et al., 2006). NGF contributes to stress-induced cutaneous hyperinnervation and influences the upstream stress response of Substance P (Babizhayev et al., 2011). For instance, NGF promotes keratinocyte proliferation and protects them from UV-induced apoptosis (Marconi et al., 2003; Pincelli et al., 1997; Wilkinson et al., 1994). Moreover, it induces the proliferation, migration, and differentiation of fibroblasts into myofibroblasts, which could be important for cutaneous wound healing (Palazzo et al., 2012). Furthermore, in melanocytes, NGF is reported to induce migration and dendricity (Peacocke et al., 1988; Yaar et al., 1991). In a stress-induced hair loss mouse model, stress exposure increased NGF expression, which enhanced the number of Substance P-positive sensory neurons, leading to the premature terminus of hair growth (Peters et al., 2004). Substance P is a pro-inflammatory neuropeptide produced by cutaneous peripheral nerve terminals in response to stress. Under stress, Substance P-positive nerve fibers were reported to be significantly enhanced (Peters et al., 2004). In the skin, it stimulates the degranulation of mast cells during stress (Singh et al., 1999), the release of several cytokines (IL-1, IL-6, IL-12) from monocytes and T-cells, leading to the proliferation of the latter, and consequent inflammation (Fan et al., 2012; Lotz et al., 1988). Interestingly, Substance P has been associated with skin microbiota dysbiosis, increasing the virulence of several microorganisms (Mijouin et al., 2013). This is properly discussed in Section 4.7.2.3. Moreover, prolactin was also reported to be immediately induced by psychological stress (Rossier et al., 1980). It stimulates keratinocyte proliferation, regulates keratin expression (Girolomoni et al., 1993; Ramot et al., 2010), and enhances sebum production in sebaceous glands (Gosain and DiPietro, 2004). Interestingly, prolactin has been reported to have immunoprotective properties during stress, due to its capacity to inhibit glucocorticoid activity (Krishnan et al., 2003). Lastly, also serotonin and melatonin (a derivative of serotonin, produced in the pineal gland), which are involved in the regulation of several mood-, behaviour-, and stress-related responses (Gomaa et al., 2017; van den Buuse and Hale, 2019), have some effects on the skin. For instance, melatonin, which is also produced in keratinocytes and melanocytes (Slominski et al., 2017), is reported to exert photoprotective action (on keratinocytes, melanocytes, and fibroblasts (Janjetovic et al., 2014; Janjetovic et al., 2017; Slominski et al., 2014)), anticancer (antimelanoma) activity, enhancement of epidermal barrier function and wound healing, skin lightening effects, anti-inflammatory activity (over atopic dermatitis, seborrheic dermatitis), hair growth stimulation, and to help in thermoregulation (reviewed in Slominski et al., 2018b). In the serotonin case, which is also produced in the epidermis and dermis, a study by Slominski et al. (2020) showed that this hormone inhibits melanogenesis, as well as the growth of healthy melanocytes and melanoma cells.

4. Impact of stress and its mediators on molecular mechanisms ("hallmarks") of aging

The mechanisms by which stress mediators affect skin aging are poorly understood. It is known that aging is dependent on several molecular mechanisms ("hallmarks"), which are the core underlying machinery of how our bodies age (López-Otín et al., 2013; López-Otín et al., 2023a; López-Otín et al., 2023b). In 2013, López-Otín et al. listed and described nine tentative hallmarks of aging, representing common denominators of aging in distinct organisms, especially mammals. These hallmarks were genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Nonetheless, ten years later, López-Otín et al., (2023a) updated their notion of these mechanisms and described three new hallmarks: disabled macro-autophagy, chronic inflammation and dysbiosis.

In this section, we have explored the impact of stress on biological aging, by describing the effects that stress and its mediators have on these aging mechanisms, specifically on genomic instability (DNA damage), telomere attrition, mitochondrial dysfunction, cellular senescence, chronic inflammation, disabled macro-autophagy, and dysbiosis. A summary of these effects is presented in Table 1.

4.1. Genomic instability (DNA damage)

The generation of harmful agents is one of the initial stages in the biological aging process. The most prevalent type of cell damage is

Table 1
Effects of stress mediators in the hallmarks of aging.

Hallmark of aging	Stress mediator	Effect / Impact	Reference Source
Genomic instability (DNA damage)	Norepinephrine and isoprotrenol	Increased DNA damage in 3T3, U2OS, and ovarian cancer cell lines	Flint et al., (2007); Flint et al., (2013); Hara et al., (2011); Lamboy-Caraballo et al., (2020)
	Norepinephrine	Decreased ROS levels and DNA damage in ovarian surface epithelial cells	Patel et al., (2015)
	Cortisol	Increased oxidative stress and impaired DNA damage repair ability in human peripheral blood and 3T3 cells	Flint et al., (2007); O'Brien et al., (1993)
	Norepinephrine, epinephrine, cortisol	Increased DNA damage and decreased DNA repair capability in 3T3 cells	Flint et al., (2007)
Telomere attrition	Norepinephrine, epinephrine, cortisol	Shorter telomere length in PBMCs	Epel et al., (2006); Tomiyama et al., (2012)
	Cortisol	Shorter neonatal telomere length	Enlow et al., (2019)
	Epinephrine	Low telomerase activity	Epel et al., (2006)
	Cortisol	Lower telomerase levels in human T-cells	Choi et al., (2008)
Mitochondrial dysfunction	Epinephrine	Enhanced mitochondrial biogenesis and oxidative damage to lipids and proteins in rat liver tissue	Napolitano et al., (2018)
	Cortisol	Increased mitochondrial biogenesis (short-term exposure); Increased ROS production and respiratory chain dysfunction (long-term exposure)	Manoli et al., (2007)
	Substance P	Improved mitochondrial function and increased ROS scavenging capacity, in mice	Yang et al., (2014)
Cellular senescence	Isoproterenol	Higher levels of p53 and p21 in heart tissue and bone marrow cells	Katsuumi et al., (2018)
		Decreased p53 in the thymus; Reduced p53 in U2OS cells and mouse embryonic fibroblasts	Hara et al., (2011)
	Norepinephrine	Induced cellular senescence features like cell flattening and SA-β-gal activity; Promoted p53 cytoplasmic accumulation	Manzella et al., (2018)
	Cortisol	Suppress SASP expression in senescent cells	Laberge et al., (2012)
	Substance P	Inhibited β-galactosidase activity in fibroblasts	Yu et al., (2020)
		Accelerated senescence and exhaustion of residual stem cells	Vitar et al., (2022)
Chronic inflammation	Catecholamines	Significant rise in blood levels of IL-6, IL-10, and CRP in humans and rodents	Kop et al., (2008); Szabó et al., (1997)
	Norepinephrine, epinephrine	Higher NF-kB and IL-6 levels in mice and rats	Bierhaus et al., (2003); DeRijk et al., (1994)
	Norepinephrine, epinephrine	Increased expression of IL-6, CRP, and TNF-α (e.g. lymphocytes, hepatoma cells)	Aninat et al., (2008); Black, (2002); Cole et al., (2010); Fu et al., (2004); Slota et al., (2015)
	Cortisol	Weaker NF-kB responses in adults	Wolf et al., (2009)
		Decreased expression of TNF-α, IL-1β, IL-10 and IL-23 inflammation markers in THP1-derived macrophages	Bongiovanni et al., (2015)
	Cortisol (lower)	Higher levels of IL-6 and TNF-α	DeSantis et al., (2012)
		Increased IL-1β production by keratinocytes	Stojadinovic et al., (2012)
Disabled macro-autophagy	Epinephrine (lacking)	Reduced hepatic levels of ATG5 in animals	Sharara-Chami et al., (2012)
	Epinephrine	Induced autophagic flux in hepatocytes and liver	Farah et al., (2014)
	Norepinephrine	Induced autophagy in gastric cancer cells	Zhi et al., (2019)
	Glucocorticoids	Promoted autophagy in many tissues (e.g., muscle, bone (osteoclasts, osteocytes), bone marrow (leukemic cells)) by increasing the transcription of autophagy genes such as ATG5, LC-3, and Beclin1	Gao et al., (2016); Grandér et al., (2009); Jung et al., (2020); Shi et al., (2015); Sinha et al., (2017); Swerdlow et al., (2008); Troncoso et al., (2014); Xia et al., (2010); Yao et al., (2013)
	Glucocorticoids (stress-levels)	Decreased autophagy in macrophages by downregulating the expression of ATGs such ATG5, ATG6, ATG7, and ATG12	Wang et al., (2017)
		Increased neuronal cell death and autophagy flux malfunction via dysregulating the AMPK/mTOR pathway, in PC12 cells	Ma et al., (2019)
	Cortisol	Promote autophagy in HeLa cells, by increasing cellular conversion of LC3-I to LC3-II	Ahn et al., (2014)
		Induced the autophagic degradation of collagen I α1 in human amnion fibroblasts	Mi et al., (2017)
	Substance P	Enhanced autophagic activity in rat BMSCs	Geng et al., (2019)

caused by the generation of reactive oxygen species (ROS), which is a mechanism shared by all respiratory life (Aschbacher et al., 2013; Polsky et al., 2022). In this line, genomic instability could be defined as a wide range of genetic lesions, promoted by extrinsic (exogenous chemical, physical, and biological agents) or intrinsic (DNA replication errors, chromosome segregation defects, oxidative processes, and spontaneous hydrolytic reactions) factors, and include point mutations, deletions, translocations, telomere shortening, single- and double-strand breaks, chromosomal rearrangements, defects in nuclear architecture, and gene disruption caused by the integration of viruses or transposons (López-Otín et al., 2013; López-Otín et al., 2023a).

According to research, chronic psychosocial stress has been related to elevated amounts of DNA damage in both people and animals. Observational human studies, for example, reveal that academic stress, bereavement, and informal caregiving are related to increased DNA damage and decreased DNA repair ability in peripheral blood (Aschbacher et al., 2013; Cohen et al., 2000; Forlenza et al., 2000; Irie et al., 2001a; Irie et al., 2001b; Knickelbein et al., 2008; Sivoňová et al., 2004). More findings have been reported in mice models, where repeated psychological stress led to increased DNA damage and decreased DNA repair across a variety of stressors (e.g., social isolation, restraint stress, forced swimming) and tissues (e.g., peripheral blood, bone marrow cells, liver, gut mucosa, brain (prefrontal cortex, amygdala, and hippocampal regions)) (Bagchi et al., 1999; Consiglio et al., 2010; Fischman et al., 1996; Fischman and Kelly, 1999; Forsberg et al., 2015; Hara et al., 2013; Nishio et al., 2007; Rentscher et al., 2022; Van Campen et al., 2002). Accordingly, mice subjected to restraint stress had an up-regulation of genes linked to DNA damage response signaling

pathways in T-lymphocytes. Nevertheless, the absolute levels of DNA damage in the cells did not alter, indicating that the damage was repaired (Flint et al., 2005).

Stress mediators impact on DNA health has also been reported. For instance, norepinephrine and isoproterenol (a synthetic catecholamine) are reported to increase DNA damage in different types of cells, comprising 3T3, U2OS, and ovarian cancer cell lines (Flint et al., 2007; Flint et al., 2013; Hara et al., 2011; Lamboy-Caraballo et al., 2020). Nonetheless, norepinephrine has been associated with decreased ROS levels and DNA damage in ovarian surface epithelial cells (Patel et al., 2015). Other studies have connected high cortisol levels to increased oxidative stress and impaired DNA damage repair ability in human peripheral blood and 3T3 cells (Flint et al., 2007; O'Brien et al., 1993). Additionally, 3T3 cells treated with norepinephrine, epinephrine, or cortisol had increased DNA damage and decreased DNA repair capability, as well as changed expression of genes involved in DNA damage or repair (Flint et al., 2007). This impact, together with elevated ROS, was also reported in several breast cancer cell lines (Flaherty et al., 2017).

4.2. Telomere attrition

DNA damage at the end of chromosomes (telomeres) contributes to aging and age-related disorders (Blackburn et al., 2015). Replicative DNA polymerases are unable to complete the copy of eukaryotic DNA telomere sections. As a result, after numerous rounds of cell division, telomeres shorten significantly, causing genomic instability and eventually leading to apoptosis or cell senescence. The reverse-transcriptase activity of telomerase, an active ribonucleoprotein that elongates telomeres to preserve their sufficient length, can avoid these negative consequences (Blasco, 2005; Chakravarti et al., 2021). Nonetheless, telomere attrition is characteristic of normal aging in humans (Blasco, 2007; López-Otín et al., 2013; López-Otín et al., 2023a).

Psychological stress impact in telomere length was first reported in 2004, revealing that mothers of children with and without disabilities who reported higher perceived stress had shorter telomeres, lower telomerase activity, and higher levels of an oxidative stress marker in PBMCs (Epel et al., 2004). Following this study, a great amount of research was conducted, which linked the different experiences of chronic stress and adversity at different stages of life (low socioeconomic status, early life adversity, and low social support) with shortened telomere length in peripheral blood leukocytes, saliva, and buccal cells (Barger and Cribbet, 2016; Chen et al., 2014; Drury et al., 2014; Mitchell et al., 2014; Mitchell et al., 2017; Mitchell et al., 2018; Rentscher et al., 2020). Moreover, research has revealed evidence of possible transgenerational effects of stress on telomere maintenance, with higher levels of maternal stress during pregnancy being linked to shorter telomere length in newborns and children (Carroll et al., 2020; Entringer et al., 2013; Marchetto et al., 2016). In another study in an animal model of chronic stress, socially isolated prairie voles produced more corticosterone, while presenting shorter telomeres and suffering increased oxidative damage (Stevenson et al., 2019).

Stress hormones have also been associated with shortened telomeres. For example, higher levels of nocturnal norepinephrine, epinephrine, and cortisol were related with shorter telomere length in PBMCs, in a study involving maternal caregivers and controls (Epel et al., 2006). Similarly, increased nocturnal levels of epinephrine following an acute stressful event, and flatter diurnal cortisol slopes were related to shorter PBMCs telomere in women caregiving for a partner with dementia (Tomiyama et al., 2012). Other studies showed that telomere attrition was related to increased epinephrine in women (Parks et al., 2009; Parks et al., 2011) and to exacerbated cortisol awakening levels in women, with the opposite tendency for men (Thomas et al., 2022). Maternal cortisol levels may also influence the telomere length of their kids, with greater cortisol production associated with shorter neonatal telomere length (Enlow et al., 2019). Interestingly, there is also some evidence that these mediators may modulate telomerase activity. In a previously mentioned study, Epel et al. (2006) also showed that women with low telomerase had significantly higher production of nocturnal epinephrine and marginally increased norepinephrine, while maintaining cortisol levels. Additionally, in an *in vitro* study, human T-cells treated with hydrocortisone at similar levels to those obtained when under stress exposure demonstrated lower telomerase levels, indicating that cortisol may inhibit telomerase enzyme activity and compromise telomere maintenance (Choi et al., 2008).

4.3. Mitochondrial dysfunction

Mitochondrial function deteriorates with age due to several interconnected factors, comprising the accumulation of mtDNA mutations, poor proteostasis leading to the instability of respiratory chain complexes, decreased organelle turnover, and alterations in mitochondrial dynamics, thus increasing electron leakage and reducing ATP generation. This condition jeopardizes mitochondria's contribution to cellular bioenergetics, increases ROS generation, and may result in inadvertent permeabilization of mitochondrial membranes, resulting in inflammation and cell death (Amorim et al., 2022; Green et al., 2011; López-Otín et al., 2013; López-Otín et al., 2023a). Logically, mitochondrial activity is essential for health maintenance, and its gradual decline leads to the aging phenotype. (López-Otín et al., 2023a).

The impact of psychological stress on mitochondrial dysfunction in cells has already been explored in some studies. Indeed, several types of chronic stress (for example, restraint stress, noise, and unexpected stress) have been linked to reduced mitochondrial function, energy production, and activity on respiratory chain complexes in rodents (Picard and McEwen, 2018a; Picard and McEwen, 2018b; Picard et al., 2014). Chronic stress, for example, caused mitochondrial damage in the brain, in mice models, by blocking respiratory chain complexes I-III and reducing mitochondrial membrane potential (Gong et al., 2011; Madrigal et al., 2001; Rezin et al., 2008). More research revealed that respiratory chain complex IV (COX) had a 0–80 % reduced activity (Picard and McEwen, 2018b). To date, in humans, several studies have connected chronic stress and adversity, including caregiving and childhood adversity, to greater mtDNA expression and free circulating mtDNA (Tyrka et al., 2016; Picard et al., 2018), and one research revealed increased free floating mtDNA in circulation following exposure to an acute laboratory stressor (Trumpff et al., 2019).

Stress hormones have also been associated with the impairment of mitochondrial function. For instance, it was reported that increased activity of the mitochondrial enzyme MAO-A during stress can boost ROS generation via catecholamine breakdown. Furthermore, evidence shows that catecholamine breakdown can result in mtDNA deletions in the adrenal medulla and cortex, and that this process accelerates with age (Neuhaus et al., 2016; Polsky et al., 2022). Moreover, in an *in vitro* model, epinephrine enhanced mitochondrial biogenesis and oxidative damage to lipids and proteins in rat liver tissue (Napolitano et al., 2018). Additionally, cortisol is thought to induce increased mitochondrial biogenesis with short-term exposure, but increased ROS production and respiratory chain dysfunction with long-term exposure (Manoli et al., 2007). Also, in research with human subjects, the binding of glucocorticoid receptors to mtDNA increased the transcription of mitochondrial genes, thereby enhancing the mitochondria's energy generation capability (Psarra and Sekeris, 2011). Moreover, also Substance P has been associated with mitochondria. For instance, Yang et al. (2014) reported that its administration was able to improve mitochondrial function as well as increase ROS scavenging capacity, in mice. Relevantly, once mitochondria get dysfunctional, they become much more susceptible to mediators like ROS and stress hormones, functioning as an aging accelerator in response to additional stress exposures (Picard et al., 2019). Regarding melatonin, it has been reported that this hormone may donate electrons to the electron transport chain, enhancing mitochondrial respiration and increasing ATP generation (Slominski et al., 2017).

4.4. Cellular senescence

Cellular senescence is a response triggered by acute or chronic damage (Gorgoulis et al., 2019), and it can be defined as a state of permanent cell growth/cycle arrest, in which cells become unable to proliferate while remaining metabolically active, coupled with stereotyped phenotypic changes (Campisi, d'Adda di Fagagna, 2007; Collado et al., 2007; Hayflick and Moorhead, 1961; Kuilman et al., 2010; López-Otín et al., 2013; López-Otín et al., 2023a). In humans, senescent cells accumulate at variable rates, ranging from 2- to 20-fold when comparing young (35 years) to old (> 65 years) healthy donors (Tuttle et al., 2020), mostly impacting fibroblasts, endothelial cells, and immune cells. Nevertheless, all cell types can undergo senescence throughout age (Xu et al., 2022), a process caused at least in part by telomere shortening with aging (Blasco, 2005). The most persuasive evidence for cellular senescence's causal involvement in aging is that the continued eradication of senescent cells increased the health span and lifespan of naturally aged mice (Xu et al., 2018).

To date, there has not been much research into whether psychosocial stress and its mediators may directly influence the formation of senescent cells and change their secretory phenotype (Polsky et al., 2022). For instance, one study in humans explored the relationship between psychosocial stress and cellular senescence and discovered that chronic stress, perceived stress, and accumulated daily stress were all linked with the expression of the $p16^{INK4a}$-encoding gene *CDKN2A*, which is a biomarker of senescence in leukocytes (Rentscher et al., 2019). Additionally, exposure to chronic stress, in mice, was shown to be related to increased p53 and with a trend towards higher $p16^{INK4a}$ expression in the liver and spleen (Razzoli et al., 2018), as well as increased $p16^{INK4a}$ and p21 expression in bone marrow leukocytes (Rentscher et al., 2022).

Some *in vivo* and *in vitro* studies have also evaluated the impact of stress mediators on cellular senescence. For example, animals given isoproterenol (a synthetic catecholamine) had higher levels of p53 and p21 in heart tissue and bone marrow cells, indicating an increase in senescent cells (Katsuumi et al., 2018). However, mice who received isoprotrenol for 4 weeks revealed decreased p53 in the thymus (Hara et al., 2011). Additionally, p53 was reduced in U2OS cells and mouse embryonic fibroblasts grown with isoproterenol every 12 hours for three days (Hara et al., 2011). Furthermore, a study by Manzella et al. (2018) showed that norepinephrine breakdown by MAO-A-activated cyclin--dependent kinase inhibitors $p21^{cip}$, $p16^{ink4a}$, and $p15^{ink4b}$, and induced cellular senescence features like cell flattening and SA-β-gal activity. Furthermore, it promoted p53 cytoplasmic accumulation. Regarding regulation of the SASP (senescence-associated secretory phenotype), cortisol was found to suppress SASP expression in senescent cells, which is consistent with its known anti-inflammatory effect (Laberge et al., 2012). Substance P has also been associated with cellular senescence. For instance, Yu et al. (2020) reported that substance P inhibited β-galactosidase activity in fibroblasts, suggesting that this substance inhibits fibroblast senescence under hyperglycemic cultures. However, excessive expression of Substance P was also related to accelerated senescence and exhaustion of residual stem cells (Vitar et al., 2022).

4.5. Chronic inflammation

Inflammation increases with age (''inflammaging''), resulting in systemic symptoms and pathological local phenotypes. Accordingly, as people age, their circulating levels of inflammatory cytokines and biomarkers (like CRP) rise (Franceschi and Campisi, 2014; López-Otín et al., 2013; López-Otín et al., 2023a). For instance, an accurate biomarker of all-cause mortality in aging human populations is elevated IL-6 levels in plasma (Hirata et al., 2020). Also, in association with increased inflammation, there is a decline of immune function (Mogilenko et al., 2021). Importantly, inflammation is a key source of cellular damage, which is thought to promote the aging process (Franceschi and Campisi, 2014).

A considerable amount of research has established direct relations between chronic psychological stress and adversity and inflammation (Polsky et al., 2022). In both observational and experimental studies, stress exposure has been linked to an increase in NF-κB transcription factor activity and the production of important inflammatory cytokines (such as IL-6, TNF-α, and C-reactive protein [CRP]), chemokines (such as MCP-1, CXCL1), and DAMPs (such as HMGB1, Hsp72) in both people and animals (Cheng et al., 2016; Fleshner, 2013; Frank et al., 2015; Glaser and Kiecolt-Glaser, 2005; Hänsel et al., 2010; Maslanik et al., 2013). Research has also shown a link between long-term stress and immune cells' glucocorticoid resistance (i.e., insensitivity to them). For instance, those who experienced more stress from loneliness and caregiving had fewer glucocorticoid receptors, decreased glucocorticoid receptor activity, increased NF-κB transcription factor activity, and increased levels of CRP, IL-1RA, and IL-6 expression (Cole et al., 2007; Miller et al., 2008; Miller et al., 2014). Also, among parents of children with cancer, greater stress was linked to a decreased ability of cortisol and dexamethasone (a synthetic glucocorticoid) to suppress IL-6 production after stimulation with lipopolysaccharide (LPS) *in vitro* (Miller et al., 2002; Walsh et al., 2018). Interestingly, early life adversity has been related to decreased cortisol levels, less glucocorticoid receptors, and enhanced CREB and NF-kB expression (Miller et al., 2009). Animal experiments have also shown that being exposed to social stressors causes splenocytes and peripheral immune cells to become glucocorticoid insensitive (Avitsur et al., 2001; Cole et al., 2009; Cole et al., 2015; Niraula et al., 2018; Powell et al., 2013; Quan et al., 2003; Reber et al., 2007; Stark et al., 2001).

Stress hormones have also been connected to inflammation. For instance, increased catecholamine expression, in response to acute stress, was related to a significant rise in blood levels of IL-6, IL-10, and CRP in humans and rodents (Kop et al., 2008; Szabó et al., 1997). Other *in vivo* research has shown that increasing doses of norepinephrine and epinephrine, especially during longer periods, led to higher NF-kB and IL-6 levels in mice and rats (Bierhaus et al., 2003; DeRijk et al., 1994). In addition, several studies using different cell types (e.g. lymphocytes, hepatoma cells) have revealed that administration of norepinephrine and epinephrine resulted in increased expression of IL-6, CRP, and TNF-α (Aninat et al., 2008; Black, 2002; Cole et al., 2010; Fu et al., 2004; Slota et al., 2015). Moreover, it has been discovered that norepinephrine modifies CD8 T-cell activation and inflammatory cytokine release (Slota et al., 2015; Strell et al., 2009). Regarding glucocorticoids, research over the years has shown their classical anti-inflammatory effect, decreasing pro-inflammatory cytokines expression in *in vivo* and *in vitro* models (Polsky et al., 2022). For example, acute social stressors led to weaker NF-kB responses in adults with higher cortisol levels (Wolf et al., 2009). Furthermore, higher levels of IL-6 and TNF-α were found in people with lower cortisol awakening responses and flatter cortisol slopes throughout the day (DeSantis et al., 2012). Also, adults who reported feeling more stressed had flatter diurnal cortisol slopes and higher levels of circulating inflammatory markers (Knight et al., 2021). Additionally, studies have shown that the intracellular production of pro-inflammatory cytokines in response to LPS stimulation *in vitro* and in *ex vivo* cells is decreased by cortisol and other synthetic glucocorticoids (DeRijk et al., 1997; Petrovsky et al., 1998; Waage et al., 1990). Furthermore, cortisol has been associated with decreased expression of TNF-α, IL-1β, IL-10 and IL-23 inflammation markers in THP1-derived macrophages (Bongiovanni et al., 2015). Concerning skin cells, Stojadinovic et al. (2012) reported that IL-1β (first pro-inflammatory cytokine released by keratinocytes on epidermal injury) production increased with cortisol synthesis inhibition. Having said that, the case of cortisol becomes quite interesting. If, on the one hand, exposure to psychological stress leads to an increase in cortisol and subsequently to the traditional increase in anti-inflammatory activity, on the other hand, that same stress can make cells insensitive to these compounds, which can cancel any positive effect. Adding to this, some research has reported that the NF-κB signaling pathway and the production of

pro-inflammatory cytokines can be activated by the binding of glucocorticoids to their receptors (Pace et al., 2007), and that dexamethasone (a corticosteroid) boosts the induction of toll-like receptor 2 (TLR-2) by TNF-α, resulting in an inflammatory immune response (Hermoso et al., 2004).

4.6. Disabled macro-autophagy

Macro-autophagy (abbreviated ''autophagy'') is the sequestration of cytoplasmic material in two-membrane vesicles called autophagosomes, which eventually merge with lysosomes to degrade luminal content (Levine and Kroemer, 2019). Autophagy decline with age is one of the most fundamental processes of decreased organelle turnover, prompting its consideration as a new hallmark of aging. Nonetheless, genes and proteins involved in autophagy are also engaged in other degradation processes, such as LC3-associated phagocytosis of extracellular material (Galluzzi, Green, 2019), and the ejection of intracellular waste (e.g., dysfunctional mitochondria) in the form of exospheres for further clearance by macrophages (Nicolás-Ávila et al., 2020). Even so, there is substantial evidence that the basic mechanism of autophagy is important to aging (López-Otín et al., 2023a).

Some studies have explored the connection between stress exposure and autophagy in mice. For instance, among mice that presented depressive-like behaviour due to chronic restraint stress, those who had their symptoms softened through agomelatine administration, presented increased autophagy, including Beclin1 and LC3-II, microglial activity marker Iba-1, and BDNF/TrkB/pERK signaling pathways (Chen et al., 2021). Additionally, chronic stress was reported to impair autophagy via Akt/mTOR signaling pathway activation (Gu et al., 2014). Interestingly, a study reports the opposite, where mice treated for depression symptoms due to chronic unpredictable stress showed decreased expression of autolysosomes, Beclin1, and LC3-II/LC3-I in the hippocampus (Zhang et al., 2020). Furthermore, another study reports that, in psychologically stressed colitis mice, psychophysical stress led to increased autophagy through upregulated expression of Beclin1, by elevating the levels of exosomal *Mir7k* (microRNA 7 k) (Tian et al., 2021).

Stress hormones have also been related to autophagy. For instance, norepinephrine and epinephrine have been shown to induce autophagy (Jung et al., 2020; Sinha et al., 2017). Indeed, epinephrine administration in neonatal rats enhanced glycogen breakdown through autophagy in hepatocytes and cardiomyocytes (Kondomerkos et al., 2005). Hepatic levels of the major autophagic protein, ATG5, were likewise reduced in animals lacking epinephrine (Sharara-Chami et al., 2012). Furthermore, epinephrine can induce autophagic flux in hepatocytes and the liver, being able to induce autophagy 1 hour after treatment, which is consistent with its role as a stress mediator (Farah et al., 2014). Additionally, norepinephrine was shown to induce autophagy in gastric cancer cells (Zhi et al., 2019). Glucocorticoids have also been demonstrated to promote autophagy in many tissues (e.g., muscle, bone (osteoclasts, osteocytes), bone marrow (leukemic cells)) by increasing the transcription of autophagy genes such as ATG5, LC-3, and Beclin1 (Gao et al., 2016; Grandér et al., 2009; Jung et al., 2020; Shi et al., 2015; Sinha et al., 2017; Swerdlow et al., 2008; Troncoso et al., 2014; Xia et al., 2010; Yao et al., 2013). Cortisol was also shown to promote autophagy in HeLa cells, by increasing cellular conversion of LC3-I to LC3-II (Ahn et al., 2014). Nonetheless, Bongiovanni et al. (2015) reported similar autophagosome numbers between control and cortisol-treated THP1-derived macrophages. Additionally, a study reported that stress-level glucocorticoids decreased autophagy in macrophages by downregulating the expression of ATGs such as ATG5, ATG6, ATG7, and ATG12 (Wang et al., 2017). Moreover, stress-level glucocorticoids increased neuronal cell death and autophagy flux malfunction via dysregulating the AMPK/mTOR pathway, in PC12 cells (Ma et al., 2019). Regarding skin cells, cortisol was reported to induce autophagic degradation of collagen I α1 in human amnion fibroblasts (Mi et al., 2017). In this line, we can conclude that glucocorticoid's impact on autophagy is concentration and cell-type dependent. Generally, low glucocorticoid concentrations activate autophagy, whereas high glucocorticoid concentrations impair it. So, based on the described findings, we may conclude that stress-level glucocorticoids lead to dysfunctional autophagy (Li et al., 2020a). Furthermore, Substance P was reported to enhance autophagic activity in rat BMSCs, thus promoting osteogenic differentiation (Geng et al., 2019).

4.7. Skin microbiota dysbiosis

In addition, skin microbiota is expected to play an important role in these mechanisms and to be affected by them since it is responsible for the homeostasis and protection of the host skin (Baldwin et al., 2017; Chen et al., 2022). Even so, López-Otín et al. (2023a) discuss this hallmark of aging, only focusing on gut microbiota, without any mention to the skin microbial flora and its potential impact on skin aging. Nonetheless, alterations in skin microbiota composition have been associated with aged skin (Abadías-Granado et al., 2021; Boxberger et al., 2021; Boyajian et al., 2021; Lee et al., 2021; Ratanapokasatit et al., 2022), but there is a lack of studies showing associations with skin aging mechanisms, which needs to be addressed in the future. Besides age, skin microbiota alterations depend on several other factors such as skin site, ethnicity, gender, skin diseases, lifestyle (UV exposure, smoking), and pollution (Boxberger et al., 2021; Lee et al., 2020; Wu et al., 2020). The current evidence of skin aging impact on its microbiota will be explored in the next subsection, summarized in Table 2.

4.7.1. Skin microbiota alterations with aging skin

In a Japanese cohort study, Shibagaki et al. (2017) reported several differences in bacterial species abundance, depending on skin site, between younger (aged 21–37 years old) and older adults (aged 60–76 years old). In this research, the older group presented a significant increase in *Corynebacterium* on the cheeks and forehead, as well as in *Acinetobacter* on the scalp and forearm. Moreover, Bacteroidetes were more abundant on aged forehead and cheek skin, while Firmicutes were significantly higher on older forehead skin. Also, higher alpha diversity was reported for the older group. On the other hand, the abundance of *Staphylococcus* in the forearm and of *Cutibacterium* on the cheek, forearm, and forehead was significantly decreased in the older group. Actinobacteria was also less abundant on aged cheek, forearm and forehead skin, consistent with the decrease in *Cutibacterium* on these skin sites, since it is the main genus belonging to the mentioned phylum. In North America, a study by Dimitriu et al. (2019) also showed that aged skin was connected with an increase in *Corynebacterium*, specifically *C. kroppenstedtii* and *C. amycolatum*, on the forehead. Jugé et al. (2018) collected skin microbiota samples from the foreheads of Western European women and the results again showed higher alpha diversity on older skin. Furthermore, taxonomic analysis revealed that the older skin had an increase in Proteobacteria and a reduction in Actinobacteria. At the genus level, aged skin showed a substantial increase in *Corynebacterium* and decreased *Cutibacterium* relative abundances. In another study, Somboonna et al. (2017) investigated the cheeks and forehead skin microbiota of 30 Thai women: 10 healthy young adults, 10 acne-prone young adults (19–24 years old), and 10 healthy older adults (51–57 years old). It was shown that Firmicutes were the most prevalent bacteria in both healthy older adults and acne-prone young adults. Gemmatimonadetes, Planctomycetes, and Nitrospirae, on the other hand, were more abundant in healthy young adults. Wilantho et al. (2017) revealed that aged facial microbiota from Thai males was characterized by bacteria of the order Rhizobiales, genera *Sphingomonas* and *Pseudoalteromonas*, as well as clinical features such as wrinkles and pores. In contrast, young adults showed an abundance of *C. acnes* and *S. epidermidis*. Howard et al. (2022) studied the skin microbiota from the forearm, buttock, and face of 158 Caucasian women aged 20—74 years. The results revealed that skin bacterial diversity increased with aging in all skin areas. Regarding the relative abundance of specific genera,

several differences were observed with age, including (i) a decrease of *Cutibacterium* and *Lactobacillus* at all body sites, (ii) an increase of *Corynebacterium* and *Enhydrobacter* on the face, (iii) an increase of *Streptococcus* and *Anaerococcus* and a reduction of *Staphylococcus* at the buttock, (iv) an increase of *Anaerococcus*, *Enhydrobacter*, and *Acinetobacter* and a reduction of *Methylobacterium-Methylorubrum* at the forearm, and (v) no changes of *Finegoldia*, *Micrococcus*, *Leptospira*, and uncultured *Neisseriaceae* at any skin site. Kim et al. (2020) studied the hands and forehead skin microbiota of 73 Korean women, divided into three age groups (10–29, 30–49, and 50–79 years old). Regarding forehead skin, Firmicutes were more prevalent within the younger group, whereas Bacteroidetes and Proteobacteria rose linearly with age. Among the studied genera, *Dietzia*, *Micrococcus*, *Leuconostoc*, *Streptococcus*, *Paracoccus*, *Acinetobacter*, and *Enhydrobacter* rose linearly with age, while no genera were diminished. Regarding hand skin, no phylum was significantly altered with age, and the genus *Leuconostoc* increased linearly in the older groups, whereas *Corynebacterium*, *Cutibacterium*, *Staphylococcus*, *Weissella*, and *Xanthomonas* decreased. Among less-explored skin microorganisms, Czepita et al. (2005) reported that the abundance of *Demodex* mites on the skin increased with age, reaching up to 95 % in adults over 71 years of age (Jacob et al., 2019). Moreover, Moissl-Eichinger et al. (2017) observed a higher abundance of *Archaea* microorganisms in individuals over 60 compared to middle-aged ones. In a very interesting and relevant study, Kim et al. (2019) studied the skin microbiota alterations in Chinese women according to functionality. From 73 individuals separated into two groups (25–35 and 56–63 years old), the study revealed that the older individuals microbiomes were developed under a larger impact of the niche-based process, with a more collapsed network of microorganisms than the younger group. Also, pathways linked with replication and repair were more prevalent in the younger group, but, among the numerous metabolism-related pathways, those connected with biodegradation were more prevalent in the older group. Li et al. (2020b) also reported that significant enrichment of nine microbial communities (i.e., *Cyanobacteria*, *Staphylococcus*, *Cutibacterium*, *Lactobacillus*, *Corynebacterium*, *Streptococcus*, *Neisseria*, *Candida*, and *Malassezia*) and 18 pathways (such as antibiotic biosynthesis) possibly influenced skin aging, signaling that skin microbiota may play essential roles in skin aging by regulating immune response, UV light resistance, and biosynthesis and metabolism of age-associated compounds. Also, in China, Li et al. (2014) studied the skin microbiota isolated from the axillary fossa of 37 healthy adults separated into two age groups (20–29 and 65–83 years old). The results showed that *Corynebacterium* spp. was significantly decreased in younger subjects, whereas no statistical differences in *Staphylococcus* spp. and *S. epidermidis* were observed. In 2014, Prohic et al. Studied the age-related variation of *Malassezzia* fungal genus on the trunk and scalp

Table 2
Skin microbiota alterations with aging skin.

Study / Reference	Demographic context	Age groups	Skin microbiota	Effect / Impact with aging
Shibagaki et al., (2017)	Japan	21–37 vs 60–76	Bacteroidetes, *Corynebacterium* *Acinetobacter* Firmicutes *Staphylococcus* Actinobacteria, *Cutibacterium*	Increase on cheeks and forehead Increase on scalp and forearm Higher on forehead Decrease on forearm Decrease on cheeks, forearm and forehead
Dimitriu et al., (2019)	North America	9–78	*Corynebacterium* (*C. kroppenstedtii* and *C. amycolatum*)	Increase on forehead
Jugé et al., (2018)	Western Europe (women)	21–31 vs 54–69	Proteobacteria, *Corynebacterium* Actinobacteria, *Cutibacterium*	Increase on forehead Decrease on forehead
Somboonna et al., (2017)	Thailand (women)	19–24 (healthy or acne-prone) vs 51–57	Firmicutes Gemmatimonadetes, Planctomycetes, Nitrospirae	More prevalent in both older adults and acne-prone youngsters (cheeks and forehead) More prevalent in healthy youngsters (cheeks and forehead)
Wilantho et al., (2017)	Thailand (men)	19–24 (healthy or acne-prone) vs 32–38 vs 51–57	Rhizobiales (*Sphingomonas* and *Pseudoalteromonas*) *C. acnes* and *S. epidermidis*	Increase on aged facial skin More abundant on young adults facial skin
Howard et al., (2022)	Caucasian women	20–74	*Cutibacterium*, *Lactobacillus* *Corynebacterium*, *Enhydrobacter* *Streptococcus*, *Anaerococcus* *Staphylococcus* *Anaerococcus, Enhydrobacter, Acinetobacter* *Methylobacterium-Methylorubrum*	Decrease on forearm, buttock and face Increase on the face Increase at the buttock Decrease at the buttock Increase on the forearm Reduction on the forearm
Kim et al., (2020)	Korea (women)	10–29 vs 30–49 vs 50–79	Firmicutes Bacteroidetes, Proteobacteria, *Dietzia*, *Micrococcus*, *Leuconostoc*, *Streptococcus*, *Paracoccus*, *Acinetobacter*, *Enhydrobacter* *Leuconostoc* *Corynebacterium*, *Cutibacterium*, *Staphylococcus*, *Weissella*, *Xanthomonas*	More prevalent in the younger group (forehead) Linear increase with age (forehead) Higher in the older groups (hand skin) Decrease in the older groups (hand skin)
Kim et al., (2019)	China (women)	25–35 vs 56–63	—	Older microbiota was developed under a larger impact of the niche-based process; More collapsed network of microorganisms in the older group Pathways linked with replication and repair were less prevalent, but those connected with biodegradation were more prevalent in the older group
Li et al., (2014)	China	20 – 29 vs 65–83	*Corynebacterium* spp. *Staphylococcus* spp., *S. epidermidis*	Increase in the axillary fossa No significant differences
Prohic et al., (2014)	Bosnia and Herzegovina	<1–82	*Malassezia furfur* *M. restricta* *M. globosa* *M. sympodialis*	Abundant on the trunk of children Prevalent on the scalp of 21–35 age group More prevalent in the 36–50 age group Dominating species on trunk of older patients
Czepita et al., (2005)	—	3–96	*Demodex*	Increasing abundance with age (up to 95 % from 71 to 96 years of age)
Moissl-Eichinger et al., (2017)	—	1–75	*Archaea*	Higher abundance in individuals under 12 and over the age of 60

skin of 100 individuals (<1–82 years old) from Bosnia and Herzegovina. The study's results revealed that *M. furfur* was abundant on the trunk skin of children, whereas *M. restricta* was found on the scalps of those aged 21–35. *M. globosa* was more prevalent in the 36–50-year-old age group, while *M. sympodialis* was the dominating species on trunk skin of older patients.

Howard et al. (2022) also studied the relationship between skin microbiota alterations and aging-related changes in host skin components (sebum, skin lipids, natural moisturizing factors, and antimicrobial peptides). For instance, facial sebaceous gland area was significantly reduced with age, and a positive correlation (Cutibacterium) or a negative correlation (*Streptococcus*, *Acinetobacter*, *Enhydrobacter*, *Corynebacterium*, *Methylobacterium-Methylorubrum*) was observed between genera relative abundance and sebaceous gland area. In 2016, Mukherjee et al. had already reported the influence of sebum on skin microbiota composition. For instance, this study showed that, with increased cheek sebum, Actinobacteria/*Cutibacterium* were more prevalent, whereas microbiome diversity decreased. The results were reversed for forehead hydration levels. These findings were consistent with Shibagaki et al. (2017), who detailed reduced sebum production with age, resulting in a lack of nutrients available for some bacteria (e.g. *Cutibacterium*) and the growth of opportunists. Regarding the major skin lipids (fatty acid, ceramides, cholesterol, and sphingolipids), results revealed that *Cutibacterium* and *Streptococcus* had a positive correlation. In contrast, *Corynebacterium*, *Micrococcus*, *Lactobacillus*, *Anaerococcus*, and *Finegoldia* had a negative correlation with lipids from all classes. Other studied components were the natural moisturizing factors and the antimicrobial peptides, also showing different correlations depending on the bacterial genera (Howard et al., 2022).

4.7.2. *Effects of stress mediators on skin microbiota*

In past years, continuous psychological stress has been shown to affect skin microbiota (Dowd and Renson, 2018; Holmes et al., 2015; Khmaladze et al., 2020; Kim and Yosipovitch, 2020), which is not surprising given that skin is one of the primary neuroendocrine organs and various cutaneous hormones and neurohormones can control bacterial physiology (Khmaladze et al., 2020). For instance, Morvan et al., (2018) studied the facial skin microbiota from 70 healthy human subjects (aged from 25 to 4 years old), which were divided into two groups according to stress level. The results revealed that in the stress group, the relative abundance and total microorganisms' number of *Corynebacterium*, *Cutibacterium* and *Staphylococcus* genera increased. In addition, lactic acid-producing bacterial genera, *Lactobacillus* and *Lactococcus*, also increased with stress, implying skin surface acidification.

The literature describes some of the effects of stress and its mediators, such as cortisol/glucocorticoids, catecholamines, and Substance P, on skin microbiota, which are summarized in Table 3.

4.7.2.1. Cortisol and glucocorticoids. Glucocorticoids, which, as previously discussed, are essential mediators of the stress response, have been reported to have a direct influence on the production of antimicrobial peptides (AMPs) by the skin (Holmes et al., 2015). For example, they are reported to decrease cathelin-related AMP and mouse β-defensin-3 antimicrobials in mouse skin (Aberg et al., 2007). Also, Krakauer (1995) and Krakauer and Buckley (2006) report that glucocorticoids decreased the effects of super antigen-activated T-cells and inhibited *staphylococcal* exotoxin-induced T-cell proliferation and cytokine secretion. Aberg et al. (2007) also showed that psychological stress exacerbated Group A *Streptococcus pyogenes* cutaneous skin infection in mice, which was related to endogenous glucocorticoid increased production. Moreover, other studies suggest that cortisol boosts the inflammatory response to *Cutibacterium acnes,* the microorganism linked to acne development and numerous other opportunistic diseases, via TLR2 stimulation (Holmes et al., 2015; Shibata et al., 2009). Interestingly, and in reverse, it has been reported that colonization with a particular strain of commensal skin bacteria stimulates local glucocorticoid production, suggesting that host-microbe interactions mediate endogenous local glucocorticoid production and are critical for skin homeostasis maintenance (Ito and Amagai, 2022; Ito et al., 2021). This was confirmed by a study that showed stimulation of CRH production in keratinocytes when exposed to *C. acnes* extracts (Isard et al., 2009).

4.7.2.2. Catecholamines. Similarly, catecholamines, especially epinephrine and norepinephrine, have also been associated with modulating skin microbiota. For instance, a study by Lyte et al. (2003) showed that incubation of *S. epidermidis* along with catecholamines (norepinephrine) resulted in increased growth and exacerbated biofilm formation. The authors suggested that the potential of catecholamines to enhance iron uptake by *S. epidermidis* could be responsible for this. Indeed, the enhanced growth of commensal bacteria like the coagulase-negative *staphylococci* (CoNS) due to catecholamine-mediated access to sequestered host iron has also been reported by Neal et al. (2001). This phenomenon has also been described for *P. aeruginosa* with a 50-fold increase in bacterial numbers (Freestone et al., 2012), and for Group A *Streptococcus* (Holmes et al., 2015; Kim and Yosipovitch, 2020). Another study by Belay and Sonnenfeld (2002) also reported the catecholamine-mediated enhanced growth of *Klebsiella pneumoniae*. Moreover, norepinephrine is reported to boost the expression of *P. aeruginosa* PA-1 attachment factor, *in vivo* and *in vitro* (Alverdy et al., 2000; Freestone et al., 2008), and both epinephrine and norepinephrine were able to increase *P. aeruginosa* biofilm formation (Cambronel et al., 2019; Freestone et al., 2012). Interestingly, catecholamines effect on *S. aureus* growth has not been consistent among studies. In fact, Neal et al. (2001) report the non-growth of *S. aureus* in the presence of norepinephrine, whereas Beasley et al. (2011) demonstrated a positive effect of catecholamines by significantly inducing the growth of staphyloferrin-deficient *S. aureus* in human serum or in the presence of human holo-transferrin.

4.7.2.3. Substance P. Substance P has also been reported to establish a link between stress and the skin's microbial flora. It has been described as having antimicrobial properties, partly by acting as an antimicrobial peptide (Hansen et al., 2006), and enhancing the production of cathelicidins and defensins (Mijouin, 2013). Nonetheless, Mijouin et al. (2013) research showed that *Bacillus cereus*, a frequent transient skin resident, may detect and respond to substance P in a way that promotes pathogenicity. In the *B. cereus* case, Substance P caused the release of superoxide dismutase, an enzyme that shields bacteria from oxidative stress, boosts bacterial synthesis of collagenase, and promotes the creation of protective biofilms. Similarly, *Staphylococcus aureus* and *Staphylococcus epidermidis* also enhanced their cytotoxicity in the presence of this stress mediator. Indeed, several other papers report that localized increases in Substance P in the epidermis can boost the pathogenicity of several bacteria, including *Bacillus* and *Staphylococci* (Moniaga et al., 2022; N'Diaye et al., 2016; N'Diaye et al., 2017). Interestingly, Substance P antimicrobial activity against *S. aureus* has been reported by Kowalska et al. (2002). Furthermore, Substance P is reported as being able to indirectly regulate *Pseudomonas*-related infections/diseases of the cornea (Foldenauer et al., 2012; Kopel et al., 2023; Lighvani et al., 2005; McClellan et al., 2008; Singh et al., 2022; Zhou et al., 2008).

Besides the previously discussed stress mediators, there are others that can impact skin microbiota. One example is acetylcholine, which is suggested to increase vulnerability to infection by *S. aureus*, *Candida albicans* and Group A *Streptococcus*, by suppressing AMPs expression and activity (Radek, 2010). Additionally, estrogen, which could be down-regulated by psychological stress (Assad et al., 2017), has been reported to increase *C. albicans* vaginal epithelial avidity and promote *C.albicans* infection in rats (Sonnex, 1998).

According to Khmaladze et al. (2020), we fully agree, "*despite the*

Table 3
Effect of stress mediators on skin microbiota.

Stress mediator	Effect / Impact on skin microbiota	Reference source
Cortisol and glucocorticoids	Decrease cathelin-related AMP and mouse β-defensin-3 antimicrobials in mouse skin; Exacerbated Group A *Streptococcus pyogenes* cutaneous skin infection in mice	Aberg et al., (2007)
	Decreased the effects of super antigen activated T-cells and inhibited staphylococcal exotoxin-induced T-cell proliferation and cytokine secretion	Krakauer, (1995); Krakauer and Buckley, (2006)
	Cortisol boosts the inflammatory response to *Cutibacterium acnes*, via TLR2 stimulation	Holmes et al., (2015); Shibata et al., (2009)
Catecholamines (epinephrine and norepinephrine)	Norepinephrine resulted in increased growth and exacerbated biofilm formation of *Staphylococcus epidermidis*	Lyte et al., (2003)
	Enhanced growth of commensal bacteria like the coagulase-negative staphylococci (CoNS)	Neal et al., (2001)
	Enhanced growth of *Pseudomonas aeruginosa* (50-fold) and Group A *Streptococcus*	Freestone et al., (2012); Holmes et al., (2015); Kim and Yosipovitch, (2020)
	Enhanced growth of *Klebsiella pneumoniae*	Belay and Sonnenfeld, (2002)
	Norepinephrine boosted the expression of *P. aeruginosa* PA-1 attachment factor, *in vivo* and *in vitro*	Alverdy et al., (2000); Freestone et al., (2008)
	Increased *P. aeruginosa* biofilm formation	Cambronel et al., (2019); Freestone et al., (2012)
Substance P	Promotes *Bacillus cereus* pathogenicity	Mijouin et al., (2013)
	Boosts the pathogenicity of several bacteria, including *Bacillus* and *Staphylococci*	Moniaga et al., (2022); N'Diaye et al., (2016); N'Diaye et al., (2017)
	Antimicrobial activity against *S. aureus*	Kowalska et al., (2002)
	Indirect regulation of *Pseudomonas*-related infections/diseases of the cornea	Foldenauer et al., (2012); Kopel et al., (2023); Lighvani et al., (2005); McClellan et al., (2008); Singh et al., (2022); Zhou et al., (2008)
Others	Acetylcholine increased vulnerability to infection by *S. aureus*, *Candida albicans* and Group A *Streptococcus*, by suppressing AMPs expression and activity	Radek, (2010)
	Estrogen increased *C. albicans* vaginal epithelial avidity and promote *C. albicans* infection in rats	Sonnex, (1998)

current knowledge in the literature, when it comes to the link between exposome, microbiome, and the skin, there is an incredible number of gaps (e.g., Sleep, diet, cosmetics) that require additional investigations that can capture these complex interactions". In this line of thought, and being exposome defined as "*the cumulative measure of environmental influences and associated biologic responses throughout the life span, including exogenous exposures and endogenous processes*" (Miller and Jones, 2014), psychological stress and its biological consequences must be included in the equation since it primarily manifests itself through human endogenous neuroendocrine pathways, which are triggered by external/-environmental factors, as previously described.

5. Oxytocin, a 'true' stress mediator?

Oxytocin, a cortisol antagonist, is a naturally occurring hormone that regulates critical aspects of the human reproductive system, as well as aspects of human behaviour (Cleveland Clinic, 2022). This hormone is primarily produced in the hypothalamus and then stored and released in the pituitary gland (Cleveland Clinic, 2022; Deing et al., 2013). Also, it has a positive feedback loop, i.e., its release in the bloodstream stimulates the pituitary gland to release it even more (Cleveland Clinic, 2022). Importantly, oxytocin is reported to decrease glucocorticoid (Benameur et al., 2021) and reactive oxygen species (ROS) (Carter and Kingsbury, 2022) levels, and it is able to make us feel more relaxed, reducing stress, thus improving skin's health (Feldman, 2021). In fact, dysregulated physiological oxytocin levels have been related to symptoms of psychological diseases such as depression, and anxiety (Meyer et al., 2020). On the opposite, oxytocin is released during positive social interactions (reviewed in Carter et al., 2008). Similarly to what happens with cortisol and catecholamines (epinephrine and norepinephrine), oxytocin and its receptor are also expressed in the skin, both being present in keratinocytes and fibroblasts (Deing et al., 2013).

Regarding the "hallmarks of aging", oxytocin has been associated with several of them. For instance, in a study with female prairie voles, Stevenson et al. (2019) reported that oxytocin treatment decreased the effects of social isolation in glucocorticoid levels, oxidative damage, and telomere attrition. In this study, it is hypothesized that these effects are due to the action of oxytocin in the hypothalamic paraventricular nucleus (PVN), inhibiting glucocorticoid activity (Neumann et al., 2000; Windle et al., 1997), by HPA activation impairment. Faraji et al. (2018) also reported that oxytocin enhancement promoted telomeres elongation. Furthermore, another study showed that oxytocin suppressed SASP and alleviated cellular senescence in natural human dermal fibroblasts (NHDFs) (Cho et al., 2019). Also, oxytocin has been demonstrated to preserve mitochondrial function in postpartum women who underwent severe childhood trauma (Boeck et al., 2018). Moreover, several studies have demonstrated the anti-inflammatory activity of oxytocin (reviewed in Bordt et al., 2019). For example, oxytocin was able to attenuate IL-6 cytokine production in THP-1 (mouse RAW 264.7 macrophage) and primary monocyte-derived macrophage cells (Szeto et al., 2008; Szeto et al., 2017). Also, it impairs microglia-mediated brain inflammatory processes by inhibiting the LPS-stimulated production of TNF-α and IL-1β (Yuan et al., 2016).

This is an unexplored area regarding oxytocin's relationship with the skin microbiota at the composition and metabolism levels, which makes it a major knowledge gap that needs to be addressed in future research.

In sum, we consider that oxytocin is not a 'traditional' psychological stress mediator since it does not pose as a direct response to it. However, oxytocin could be relevant for managing stress effects on human health, and for that reason its role on skin cellular aging mechanisms and skin microbiota should be explored. To date, we know that oxytocin can impair glucocorticoid activity; nonetheless, it matters to understand if its anti-stress effects are also due to a direct impact on skin cells and microbiota.

6. Conclusions

Across the years, it has become clear that psychological stress poses a serious threat to human health and well-being, acting, for example, as a bogy-aging catalyst. Besides that, several diseases, like heart conditions and depression, have also been associated with it. Stress is mediated by several hormones (e.g., cortisol, epinephrine, and norepinephrine), which exert a direct impact on skin health and function. Besides these hormones, also oxytocin, a non-traditional stress mediator and cortisol

antagonist, has been explored. In fact, its relationship with psychological stress and the "hallmarks of aging" has been documented in literature. At the cellular level, it has been proved that these hormones affect some aging-related molecular mechanisms ("hallmarks of aging"), such as genomic instability (DNA damage), telomere attrition, mitochondrial dysfunction, cellular senescence, chronic inflammation, disabled macroautophagy and dysbiosis. The main issue here is that the majority of these effects, with the exception of oxytocin, tend to accelerate the aging process. Nonetheless, regarding skin aging, there is still a lack of research which needs to be addressed. Focusing on dysbiosis, specifically on skin microbiota which is one of the main topics of this paper, we can conclude that the above-mentioned stress mediators have some effects on skin microbiota. Additionally, several skin microbiota compositional changes have been related to the natural aging process. However, the knowledge gaps on these topics are huge. First, the majority of the papers that report connections between skin microbiota and skin aging are conducted on Asian communities and, therefore, some differences are expected to be found depending on the racial group. Also, there is a lack of research regarding compositional and metabolic changes of skin microbiota when in contact with these stress hormones. Moreover, it matters to question if these potential alterations affect the aging molecular mechanisms. Ultimately, it is important to understand if skin microbiota is a relevant 'player' in the stress-induced skin aging processes.

Conflict of interests statement

The authors have no conflict of interest to declare.

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CRediT authorship contribution statement

Marco Duarte: Writing – original draft, Conceptualization. **Ana Madureira:** Writing – review & editing, Supervision, Conceptualization. **P. Raaj Khusial:** Writing – review & editing, Supervision, Conceptualization. **Sílvia Santos Pedrosa:** Writing – review & editing, Supervision, Conceptualization.

Data Availability

No data was used for the research described in the article.

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