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Review

Psychological Stress and skin aging: A review of possible mechanisms and potential therapies

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Abstract

The link between psychological stress and aging is intuitive although the underlying mechanisms are not well defined. Evidence suggests that chronic psychological stress stimulates the autonomic nervous system, renin-angiotensin system, and the hypothalamic-pituitary-adrenal axis when the body attempts to resolve perceived threats to homeostasis. Prolonged activation of these pathways can result in chronic immune dysfunction, increased production of reactive oxygen species, and DNA damage, which are known to contribute to the again of skin and other tissues.

Despite the lack of conclusive evidence directly linking psychological stress to skin aging, mechanisms by which stress leads to immune dysfunction, oxidative radicals, and ultimately DNA damage via neuronal, endocrine, and immune modulation may present a possible intervention for skin aging. In addition to the wide array of anti-oxidant therapies being developed to combat aging, the topical use of beta-blockers such as timolol, angiotensin receptor blockers such as valsartan, glucocorticoid blockers such as mifepristone, and cholinergic modulators including botulinum toxin, might be potential therapeutic strategies to prevent skin aging. Given the current understanding of these pathways, it would be premature to utilize such modalities for prevention of skin aging at this time, but future research into this type of topical pharmacologic anti-aging intervention may be promising.

Key Words: Psychological stress, anti-aging

Introduction

This review will cover a diverse array of systems that are likely to connect the phenomenon of psychological stress to aging of the skin and based on these possible connections will speculate on potential novel skin anti-aging interventions. Although direct evidence linking psychological stress to aging is still emerging, the effect of psychological stress on the autonomic nervous system, renin-angiotensin system (RAS), and hypothalamus-pituitary-adrenal (HPA) system is well established. These systems are known to contribute to inflammation, oxidative stress and DNA damage, which are known aging mechanisms in all tissues including the skin.

Methods

Studies were identified by searching Pubmed MEDLINE. The search strategy was based on the concepts of "stress", "skin", and "aging" with multiple subject headings and text words to describe each concept. They include terms such as psychological, emotional, ethnicity, senescence, infection, cancer, and disease. No year limits were applied to the searches and therefore included the full year range of the database up to September 2011, when the search was conducted. No language limits were applied although only English-language studies were reviewed.

Results

The connection between stress and aging

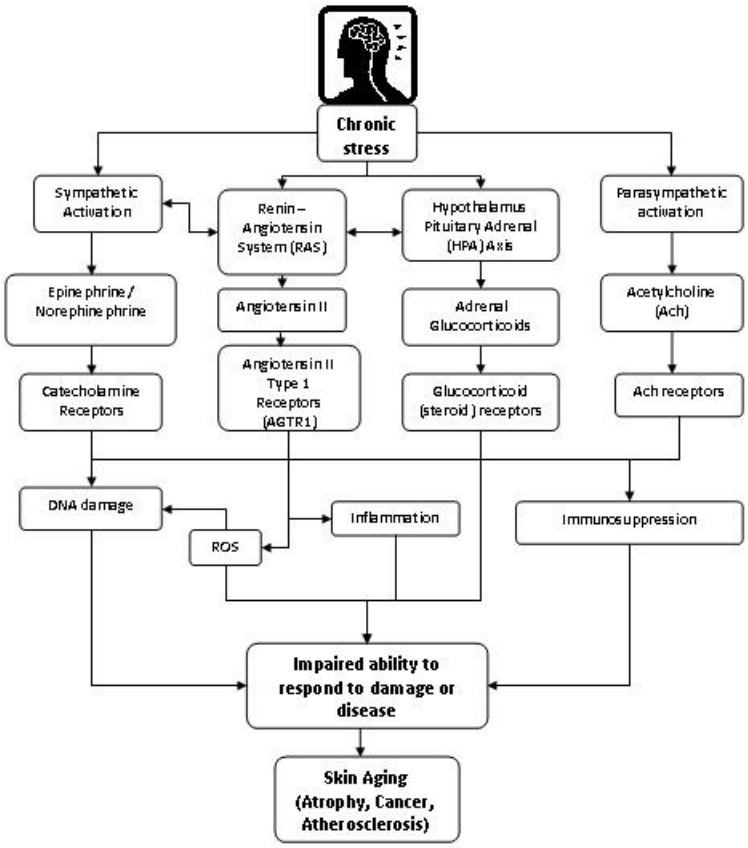
Biological aging is a process of progressive decline in organismal fitness and cellular function, which contribute to the development of age-related diseases and eventual death [1]. Theories of aging center around models relating free-radical formation, immune dysfunction, and cumulative DNA damage [2]. Several diseases commonly considered as models for aging [diabetes, atherosclerosis, rheumatoid arthritis, osteoporosis, and the progeroid syndromes] are also characterized by pathophysiology involving imbalances of reactive oxidation species formation, innate and adaptive immunity, and DNA damage/repair processes [2-17]. Furthermore, chronic immune dysfunction and reactive oxidation species (ROS) inhibit genetic and cellular repair, contributing to a synergistic and cumulative decline in cellular and physiological function [18].

Stress is the phenomenon in which a potentially harmful stimulus results in a physiological or psychological disturbance to homeostasis [19-21]. Psychological stress can modulate the body's defenses, depending on such factors as the duration of the stressful condition, as well as the individual's reaction to or perception of the situation [22]. In attempting to preserve homeostasis, the body activates several well-known mechanisms in response to psychological stress including the "fight-or-flight" sympathetic adrenal medullary (SAM) pathway, the renin-angiotensin system (RAS) pathway, the hypothalamic-pituitary-adrenal (HPA) pathway, and the parasympathetic (cholinergic) pathway [20, 23, 24].

The body initially responds to stress by activating the autonomic nervous system to release catecholamines (e.g. epinephrine and norepinephrine) from the adrenal medulla and by triggering the pituitary gland to release a surge of adrenocorticotrophic hormone (ACTH), which causes the adrenal cortex to release glucocorticoids (cortisol). This has been studied and quantitatively measured in a number of studies dating back to the 1970s. For example, human studies have shown that stressful situations including puzzle solving, mental arithmetic, novel environments, or threatening presences result in rising levels of catecholamines, angiotensin, cortisol, and acetylcholine [25, 30-36]. Studies in animals similarly demonstrate that exposure to temperature extremes, predators, sleep deprivation, or immobilization increase catecholamine, angiotensin, cortisol, and acetylcholine release [20, 32-34, 36-38].

Skin aging

Skin aging is a function of both chronological aging and photoaging [29]. Both chronological and photoaging are cumulative processes. However, photoaging is primarily a function of sun exposure and pigmentation, whereas chronological aging is primarily a function of time [29]. Although psychological stress is presumably a component of chronological skin aging, evidence directly connecting psychological stress to skin aging is limited. What can be demonstrated, however, are proven mechanisms by which psychological stress can lead to neurological, endocrine, and immune changes and how these changes cumulatively contribute to the common mechanisms by which aging is known to occur (See Figure 1).



The skin and nervous system are both derived from the same primary germ layer during embryonic development and skin cells express proteins that are also common to neuronal signaling pathways [23, 25]. For example, acetylcholine (Ach) is a ubiquitous neurotransmitter in the central and autonomic nervous system that is also involved in immunomodulation of the skin. Proteins responsible for Ach signaling, synthesis, and degradation are also found in keratinocytes and mast cells [23, 25]. Moreover, melanin is a downstream product of phenylalanine, the essential amino acid fundamental to dopamine, epinephrine, and norepinephrine synthesis; proteins responsible for catecholamine and melanin metabolism are found in melanocytes [26]. Melanin production is furthermore stimulated by melanocortin as well as ACTH, a hormone that is produced in the pituitary [27, 28]. So it is perhaps not surprising that central nervous system activities can also modulate cellular function in the skin [20, 23, 25].

From this basic overview of the link between psychological stress and modulation of catecholamines, angiotensin, glucocorticoids, and acetylcholine this review will now shift focus to the mechanisms by which these molecules can lead to skin aging and potential skin anti-aging interventions that modify these pathways.

Psychological Stress, the Sympathetic Adrenal Medulla pathway, and DNA damage--Psychological stress activates the autonomic nervous system to trigger release of catecholamines [e.g. epinephrine and norepinephrine] from the adrenal glands [19, 20, 39]. In the short term, epinephrine and norepinephrine increase pulse, respiratory rate, and blood pressure. But over the long term, these catecholamines can have many negative effects on the body [24]. Among other problems, long-term increases in catecholamines can cause DNA damage, immunosuppression, tumor growth, dementia, and cardiovascular disorders [18, 19, 40-45].

The mechanisms by which stress-induced catecholamine release causes DNA damage and immunosuppression are perhaps the most well defined molecular pathways linking stress and aging [19, 45]. A recent report demonstrated that catecholamines, working through β2-receptors, result in DNA damage [19]. It is important to note that in this model for chronic psychological stress, mice were continuously infused for four weeks with the β2-receptor-agonist isoproterenol, a synthetic analogue of epinephrine. The group found that prolonged isoproterenol infusion damages histones, which are the primary protein component housing DNA in the nucleus. Furthermore, it was shown that isoproterenol infusion leads to DNA damage specifically in the thymus, an immune organ, which reacts prominently to acute and chronic psychological stress. Moreover, this study demonstrated isoproterenol infusion leads to decreased levels of p53 in the cells of the thymus. This is significant because p53 is a protein that is well established to be involved in genome protection and maintenance by preventing proliferative gene expression, DNA mutations, and cell division and is implicated in etiology of various types of cancer, including skin cancer [19,

46-49]. The study authors further suggest that this mechanism may just be one of several by which chronic stress in the form of persistent catecholamine excess may contribute to DNA damage. From a medical standpoint, this study is interesting because a wide-variety of beta-2 [β2] blockers are currently utilized for treatment of cardiovascular disease and have been suggested as a potential therapeutic option to promote wound healing in the skin [50, 51].

Acute vs. Chronic Stress: The catecholamine system--There is an important distinction between acute and chronic stress in terms of how the body maintains homeostasis. Acute stressors are thought to be beneficial whereas chronic stress is thought to be detrimental to the body's ability to fight disease, maintain homeostasis, and prevent aging. Acute stress is thought to mobilize immune cells, promote their migration to damaged tissues, and increase both cellular and humoral adaptive immunity [21, 22, 24, 52-59].

Although acute stress is beneficial in such situations as recovery from wounds or infection, it is generally accepted that protracted stressful conditions [chronic stress or repeated episodes of acute stress] have the opposite effect, namely immunosuppression, leading to increased infections and diseases [1, 20, 22, 24, 45, 60-70]. In a healthy person, for example, epinephrine released in response to acute stress has a stimulatory effect on chemotaxis, which may prepare the immune system to respond to pathogens [22, 71, 72]. In chronically stressed individuals, however, persistent adrenergic stimulation continuously mobilizes immune cells without rest. When an acute stress arises in this abnormal setting, catecholamine stimulation is unable to provide a boost to chemotaxis when it is most needed [20, 22, 24, 73-75].

Acute vs. Chronic Stress: The renin-angiotensin system--The renin-angiotensin system [RAS] is activated primarily in response to decreased renal blood flow, but is also activated by signals generated from the sympathetic and HPA systems in response to physical or psychosocial stressors [20, 34, 35, 76]. The physiology of the RAS begins with juxtaglomerular cells of the kidney that release renin, which in turn activates angiotensin II to cause vasoconstriction, release of aldosterone and antidiuretic hormone, and other downstream effects. Prolonged or repetitive stress-induced activation of RAS may lead to vascular inflammation and atherosclerosis [20]. Inflammatory cells commonly express the angiotensin II type 1 receptor [AGTR1] and it has been shown that angiotensin II modulates the behavior and distribution of inflammatory cells [20, 77]. Inflammation is a component of the initiation and progression of atherosclerosis and prolonged activation of RAS may contribute to immune-mediated vascular damage [20, 78, 79].

Angiotensin II exerts its effects through a variety of intracellular mechanisms. Working through AGTR1, protein kinase C [PKC] and Janus kinase [JaK] pathways, angiotensin II stimulates monocytes and macrophages to increase the production of various cytokines and inflammatory mediators [20, 80-89]. Prolonged activation of the RAS may also lead to cancer tumorogenesis; angiotensin II has been shown to promote angiogenesis and invasion in melanoma and breast cancer cell lines [90-92].

The renin-angiotensin system and oxidative stress--Angiotensin II can stimulate NADPH-oxidase-dependent ROS production in neutrophils through several molecular pathways including MAP kinase, ERK, and phospholipase A2 [20, 93-95]. Angiotensis II also inhibits the synthesis of the antioxidant heme oxygenase-1 in human neutrophils [20, 96]. Oxidative stress also plays an important role in chronological and photoaging in the skin [97-102]. In normal unstressed cells, there is a balance of reactive oxygen species (ROS) production from the mitochondria and expression of antioxidant enzymes, including catalase, superoxide dismutase (SOD), and glutathione peroxidase [103, 104]. When a cell comes under stress, however, this balance is disrupted and the unchecked free radicals can alter cellular behavior [103, 105, 106]. Diminished antioxidant capacity in the face of increased ROS also activates the transcription of NF-κβ, which promotes transcription of a variety of inflammatory and proliferative genes [17, 79, 107]. Angiotensin II itself can also directly increase NF-κβ activity [20, 89].

The end result of these pathways is an imbalance of oxidative free radicals with resultant DNA damage and increased expression of proliferation genes and inflammatory cytokines, which can lead to aging and age related diseases such as cancer and atherosclerosis [2-17]. Inhibiting angiotensin II or the AGTR1 receptor has been demonstrated to block these ROS generating pathways. Valsartan blockade of the AGTR1 receptor significantly decreases ROS generation in neutrophils isolated from human subjects [20, 108]. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers also decrease NF-κB DNA binding activity in monocytes, neutrophils, and endothelial cells [20, 83, 108] (See Figure 1). These findings are interesting given the variety of angiotensin receptor blockers (e.g. Valsartan) that are currently utilized for treatment of cardiovascular disease. Moreover, in vitro and observational studies show that ACE-inhibitors and angiotensin receptor blockers can inhibit several types of cancer, including skin cancer [109-111]. A large 2008 cohort study of patients at high risk for basal cell and squamous cell carcinoma found that patients using a systemic ACE-inhibitor or angiotensin receptor blocker developed these cancers at a significantly lower rate than non-users. Although this study did not demonstrate causality, the authors speculate that

the association results from blocking angiotensin pathways because other anti-hypertensive medications did not have the same effect [109].

Stress and the HPA axis--The hypothalamic-pituitary-adrenal (HPA) axis responds to psychological or physiological stress by secreting corticotrophin releasing hormone [CRH] and ACTH, mediating a release of glucocorticoids from the adrenal cortex [22]. Under conditions of chronic stress, persistently high levels of glucocorticoids have many negative effects including immunosuppression, tissue atrophy and acceleration of the aging process in nearly all tissues including skin [24, 112-114]. Glucocorticoid excess, either from exogenous medication or endogenous disease [e.g. Cushing's syndrome] has several deleterious effects on the skin [115]. Glucocorticoids can cause atrophy and impaired wound healing by interfering with keratinocyte and fibroblast function [115-118]. This results from suppression of hyaluronan synthase and depletion of glycosaminoglycans, as well as reduced collagen and lipid production. These structural transformations clinically manifest as atrophy and thinning of the skin, increased transepidermal water loss related to disruption to the skin permeability barrier, and easy bruising with impaired wound healing [115-122]. Of note, these effects are similar to aging of the skin in the geriatric population [123, 124].

At the molecular level it is thought that glucocorticoids mediate these effects through a variety of mechanisms mediated by the intracellular glucocorticoid receptor [GCR][118]. Glucocorticoid binding to the GCR results in its translocation to the nucleus, where it modulates transcription either by directly binding to DNA or through protein-protein interactions with transcription factors themselves [118, 125, 126]. Among the transcription factors affected are activator protein-1, Smad3, and NF-κβ [127-129]. Genes affected by these interactions include those needed for lipid synthesis as well as production of extracellular matrix proteins [collagens, proteoglycans and elastins] [118, 130, 131].

Perhaps not surprisingly, glucocorticoid blockers have also been shown to prevent psychological stress-induced changes in skin structure and function. A 2006 study exposed hairless mice to psychological stress in the form of continuous visible light and radio noise for 48 hours. The authors reported that GCR blockade with mifepristone [Mifeprex®] as well as CRH receptor inhibition with antalarmin prevented or reversed several psychological stress-induced skin abnormalities including keratinocyte proliferation, permeability barrier homeostasis, and stratum corneum integrity [132].

Stress and the Cholinergic Pathway--Less is known about the relationship between stress, cholinergic signaling, and aging. The parasympathetic nervous system activation mediates a variety of functions, including muscle contraction and glandular secretion, as well as changes in cell proliferation and migration [23, 133, 134]. Activation of the parasympathetic nervous system releases acetylcholine (Ach) from nerve fibers, which activates nicotinic ACh receptors and/or muscarinic ACh receptors in target organs [23, 25]. Immune cells, including dendritic cells, mast cells, neutrophils, and macrophages, possess the components of cholinergic signaling pathways [23, 135]. Localized cholinergic signaling can also suppress of skin immunity, resulting in infections and delayed wound healing [23, 26, 136]. Dysregulated keratinocyte production of antimicrobial peptides such as cathelicidin and defensin resulting from persistent Ach activity can contribute to a variety of diseases including bacterial infection as well as atopic dermatitis, psoriasis, and pemphigus [23, 121, 137, 138]. Although studies of anticholinergic medications for prevention of skin aging are lacking, a wide variety of anticholinergic drugs are currently utilized in dermatology, including topical antihistamines such as diphenhydramine, oxybutynin (hyperhidrosis), and botulinum toxin.

Discussion

The data reviewed here illustrate that psychological stress activates the SAM, RAS, HPA and cholinergic systems, which contribute to immune dysfunction, ROS, and DNA damage [19, 20, 25, 132]. Moreover, the known mechanisms by which immune dysfunction, ROS, and DNA damage contribute to senescence are intriguing from the viewpoint of aging intervention [2-17]. Cumulative damage to cellular and DNA repair mechanisms play a role in the declining ability of the body to repair itself. Substantial evidence demonstrates that synergistic and cumulative DNA damage caused by inflammation and oxidative free radicals results in part from a progressive age-related failure of cellular maintenance and repair systems to respond appropriately to cell stress [1, 139-145]. Furthermore, oxidative stress specifically damages promoters for the genes responsible for cellular maintenance, including antioxidant and DNA repair enzymes [18]. In the skin, unchecked free radicals can destroy cells and cellular components including collagen and elastin fibers resulting in formation of furrows and wrinkles and skin disorders including cancer [97-102].

Although acute mild stress-induced stimulation (hormesis) of these repair mechanisms, including exercise, caloric restriction, and brief UV irradiation, is recognized as having anti-aging effects [1, 139, 146-148], chronic or repetitive stress exacerbates aging through cumulative processes of inflammation, oxidative stress and DNA damage [3, 149-153]. Prolonged activation of the

sympathetic, RAS, HPA, and parasympathetic systems owing to chronic stress may result in suppression of the immune system's ability to appropriately respond to acute psychological stressors [20, 23].

Crosstalk between neuronal, endocrine, and immunologic systems is also postulated to regulate how the skin responds to acute versus chronic stress, which can modulate its response to injury and disease [20]. Repetitive cycles of chronic stress, inflammation, and disease in concert with persistent stress-induced catecholamine and glucocorticoid excess may result in diminished keratinocyte and fibroblast function that underlies the aging process of the skin [60, 112, 152-162]. See Figure 1.

As mentioned above, the somewhat paradoxical phenomenon in which chronic stress causes immunosuppression in the setting of a low-grade inflammatory state might be explained by interaction between the HPA and renin-angiotensin system [RAS]. Whereas glucocorticoids are known to be broadly immunosuppressive, renin and angiotensin released in response to chronic stress may allow for a pro-inflammatory state to exist in the setting of immunosuppression [20, 21, 163]. In other words, persistent glucocorticoid elevation broadly suppresses the immune system. But simultaneous chronic activation of the RAS may allow for a low-level inflammatory state to exist even while the adaptive immune response remains suppressed by persistent glucocorticoid release [20, 21, 127-129, 164]. The net result may be a situation in which persistent release of pro-inflammatory cytokines cause indiscriminate skin damage that is compounded by the failure of the adaptive immune system to specifically respond to infection or disease. In the context of chronic stress, cholinergic suppression of antimicrobial activity in the setting of catecholamine and glucocorticoid-induced immunosuppression as well as angiotensin-induced inflammation may further contribute to the phenomenon of a persistently active but ineffective and deleterious immune response [21, 25, 165].

There is currently an abundance of research focused on skin anti-aging therapy including vitamins, resveratrol, retinoids, estrogen agonists, anti-glycation compounds, and polyphenols [166-177]. Could beta-blockers, angiotensin receptor blockers, glucocorticoid antagonists, or cholinergic modulators be added to the current list of candidates with potential for fighting skin aging? From a dermatology point of view, it is a provocative idea. Because stress can lead to prolonged catecholamine, angiotensin, glucocorticoid, and cholinergic activity and because prolonged activity of these hormones is associated with aging and age-associated disease, we might prevent or delay skin aging by topical application of one or more of these FDA-approved drugs. The potentially beneficial medications would include beta-blockers, angiotensin receptor blockers, glucocorticoid receptor antagonists, or anticholinergics. The idea that systemic drugs developed for non-dermatologic indications may have a dermatologic application is not new. The beta-blocker propranolol is systemically used for treatment of vascular tumors in the skin [178-180]. The systemic anticholinergic oxybutynin [Ditropan®] blocks muscarinic Ach receptors and was developed for urge incontinence, but is now prescribed for hyperhidrosis [181, 182]. Finasteride [Propecia®], an anti-androgenic hormone initially developed for prostate hypertrophy, is also used for pattern alopecia [183].

Moreover, topical formulations of medications are known to have benefits that were initially noted as side effects. The antihypertensive minoxidil [Rogaine®] is now used topically for treatment of alopecia [184]. The beta-blocker timolol [Timoptic®] is commonly used for topical treatment of glaucoma [185]. The prostaglandin analog bimatoprost [Latisse®] was, in turn, developed for treatment of glaucoma, but is now used to darken and lengthen eyelashes [186]. Additionally, the use of topical precursors to aspirin, a non-steroidal anti-inflammatory drug [NSAID] for prevention of skin aging have been studied with promising results [187].

Conclusion

As the fundamental molecular pathophysiology underlying various disease processes including aging becomes better understood, it seems more plausible that currently available modifiers of these stress-related hormonal pathways may be useful for prevention of skin aging. For example the molecular pathophysiology underlying psoriasis and atherosclerosis, two diseases, which are known to be exacerbated by stress, have been shown to have many similarities [188, 189]. Furthermore, ACE inhibition, mineralocorticoid blockade, and beta-blockade can slow and potentially reverse age and congestive heart failure-associated cardiavascular remodeling, a process characterized by collagen degradation, apoptosis, and fibrosis [190, 191]. Skin manifestations of various stress-related gastrointestinal, renal, and neurological diseases are also well known. Thus it seems at least conceivable that drawing a parallel between age-related disease pathways may potentially yield new avenues for therapeutic intervention with both cosmetic and clinical medical applications.

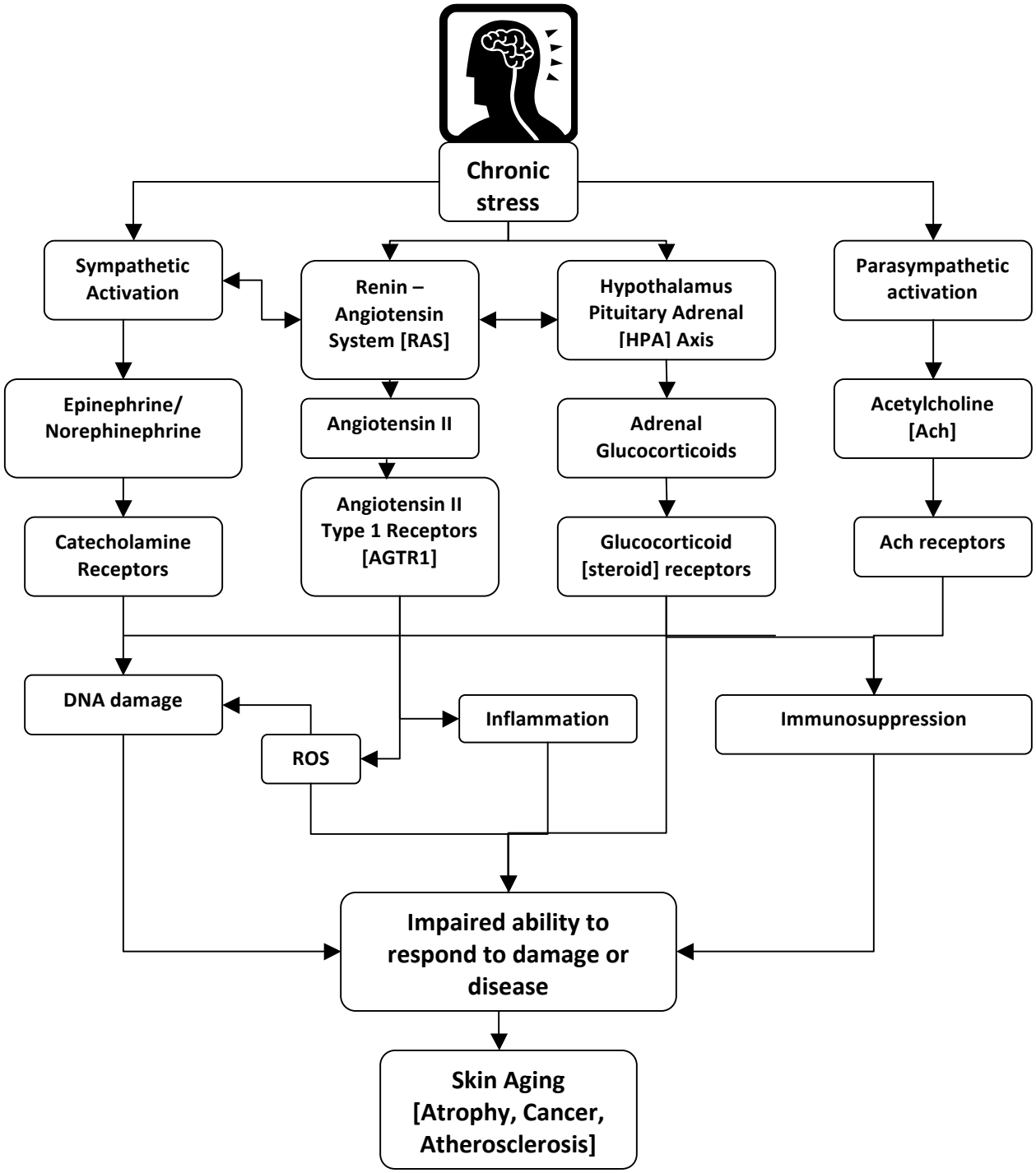


Figure 1. Hypothetical pathways linking chronic psychological stress with skin aging [19-21, 23, 25].

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