

Skin aging: Neuroendocrine challenge

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ABSTRACT

Introduction. Skin is deeply affected by aging as all the organs do, including endocrine glands and neuroendocrine circuits. The anomalies of aging are connected to the internal aspects including hormonal panel mostly vitamin D status and glucocorticoid axes integrity, melatonin networking, thyroid function, and catecholamines/serotonin release), state of health/illness, genetic background and bio-neuroendocrine/neurotransmitters pathways as well as immune defence. Moreover, external environment elements like sun exposure, radiations, pollution, physical, chemical and biological agents are consistent with internal mentioned aspects. Our purpose is to provide a mini-review regarding neuroendocrine and endocrine perspective of skin aging. Particular aspects on glucocorticoids, vitamin D and 5-hydroxytryptamine are pointed out. This is a narrative type of review. Skin is situated at the crossroad between intrinsic and extrinsic aging and the neuroendocrine approach is essential for understanding its time dependent changes.

Keywords: skin, endocrine, neuroendocrine, glucocorticoid, 5-hydroxytryptamine, vitamin D

Abbreviations: ACTH = adrenocorticotrophic hormone, UV = ultraviolet

INTRODUCTION

Skin is deeply affected by aging as all the organs do, including endocrine glands and neuroendocrine circuits (1). The time dependent complex equation normally involves a certain level of dys-function, loss of integrity and a damaged capacity to stress response regardless the type of stress (1). The anomalies of aging are connected to the internal aspects including hormonal panel mostly vitamin D status and glucocorticoid axes integrity, melatonin networking, thyroid function, and catecholamines/serotonin release, the state of health/illness, genetic background and bio-neuroendocrine/neurotransmitters pathways as well as immune defence (1) (Figure 1). Moreover, external environment elements like sun exposure, radiations, pollution, physical, chemical and biological agents are consistent with internal mentioned aspects (1).

Skin represents the strategic cut-off between internal and external world, being appreciated as the largest organ of the human body but also it represents a major neuro-endocrine-immune organ (2). The epidermal and dermal cells respond to neuroendocrine mainstream through their receptors (2). The local response is to neurotransmitters, cytokines, and hormones based on local receptors (2). The circuits involve paracrine, endocrine and neuroendocrine parameters (2). Skin has numerous receptors to internal and external stimulus; it is self-regulated through bidirectional coordination and feedback (3). Ultraviolet (UV) action of tegument surface causes its absorption converting an electromagnetic wave into a chemical reaction including generation of local cytokines, urocortins, enkephalins, and activation of ACTH (adrenocorticotrophic hormone) – cortisol axes and vitamin D absorption (3). UV type B is more potent than type

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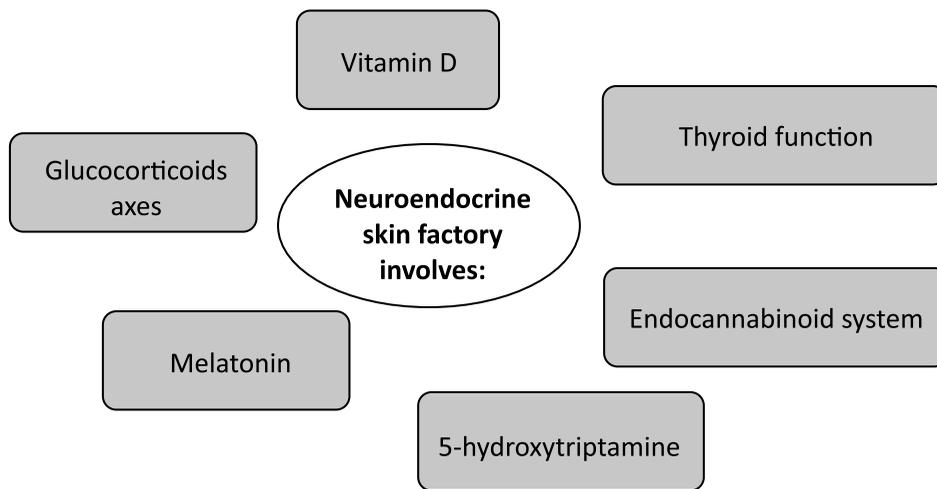


FIGURE 1. The neuroendocrine networking involving the skin aging

A (3). The circuits of response are hierarchical (4). They suffer anomalies during the aging process including the way of response and further on the way skin generates commands (4). Controversies around skin aging are still running, for instance, stress is a general term that involves the activation of different mechanisms or the blockage of others and the particular types of response are altered during time whether is physiological or pathological (5). Acute stress releases catecholamines and chronic exposure to stress induces persistent hypercorticism (5). Overall, skin is the crossroad between intrinsic aging (chronological) and extrinsic aging (like photo-aging) (6).

AIM

Our purpose is to provide a mini-review regarding neuroendocrine and endocrine perspective of skin aging. Particular aspects on glucocorticoids, vitamin D and 5-hydroxytryptamine are pointed out.

METHOD

This is a narrative type of review. The search words are “neuroendocrine”, “skin aging”. A selection of 33 papers represents the included articles.

GENERAL DATA PRESENTATION

Glucocorticoid axes

The hypothalamic-hypophyseal-adrenal axis involves steroidogenic production and further on the glucocorticoids exert a multi-organ action at every organ of human body including the skin (4). From

some point of view, skin is a steroidogenic target and site since CYP11A1 is the local enzyme capable of converting cholesterol to a derivative like pregnenolone which is then driven into human body at different steroidogenic tissues and it is converted to other steroids metabolites (4). Also, at skin level CYP11A1 catalyzes the conversion of 7-dehydrocholesterol to 7-dehydropregnenolone and further on to vitamin D if UVB action is positive (downstream with CYP27B1, A1 and CYP24A) (4). Also CYP11A1 is situated on the pathway of lumisterol (4). Circadian rhythm is also reflected at skin level as dictated by hypothalamic pacemaker in addition to pineal gland that normally controls body temperature, food and water intake, cardiac rhythm etc. (7). The local skin cells have, however, independent cycles of circadian (for 24 hours) and ultradian (less than 24 hours) that integrate different stimulus (7). Collagen, the key component of the skin responsible for elasticity and integrity, is damaged in autoimmune conditions and pathological excess of glucocorticoids that also modulate the immune response inclusive at skin level (8). Chronic stress associates persistent hypercortisolemia which induces an alteration of skin homeostasis (8). Generally, there is an increasing incidence of metabolic complication through lifespan and type 2 diabetes mellitus, obesity, hyperlipemia causes not only cardiovascular disorders, skeleton alterations, but also a damaged elasticity and repair program of the skin in association with chronic infections, alterations of wound healing etc. (9,10). In metabolic syndrome (with an age-dependent pattern of incidence) there is reactive hypercorticism which is different from Cushing’s syndrome (11). Somewhere in the middle, between frank Cushing’s syndrome and in-

tact glucocorticoid axes, there is subclinical Cushing's syndrome (a terminology that is no longer encouraged nowadays) (12,13). One third of adrenal incidentalomas have persistent autonomous cortisol secretion (13). Adrenal incidentaloma has an age-dependent pattern, opposite to pituitary incidentaloma which can be found also in youth without a severe clinical significance (14,15). Cushing's syndrome affects the skin causing striae, acne, virilisation in females etc. (16). Adequate therapy by tumour removal in endogenous cases partially reverses dermatological manifestations (17,18).

Vitamin D system

Vitamin D, the element that ensures the health of bone and muscles, is essentially related to the skin since its synthesis start here (80% of endogenous origin) (19). 7-dehydrocholesterol is the basis of synthesis; then two more steps of activation are at the level of liver and kidney (19). Parathormone (PTH) regulates its intestinal effect of stimulating calcium absorption, the role in skeletal health, and the conversion of 25-hydroxyvitamin D to calcitriol at the level of renal cortex (20). Vitamin D receptor is distributed in all tissues including in the skin, thus its role in cardio-metabolic conditions as well as different cancers but also dermatological conditions like psoriasis, atopic dermatitis, alopecia etc. (21). Aging involves lower sun exposure thus inherent lower vitamin D synthesis (21). Changes caused by chronic exposure to oxidative stress, for instance due to photo-exposure, induce local deterioration (22). The effect is not only on vitamin D synthesis but also on DNA repair, RNA function and proteins metabolism (22).

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Serotonin and skin

5-hydroxytryptamine (serotonin) release is related to climacteric syndrome in peri-menopause with transitory flushes and increase body temperature (23). Moreover, the tryptophan derivate product negatively influence bone biology especially in addition to a time dependent bone loss (24). Excessive 5-hydroxytryptamine is pathologically found in carcinoid syndrome with flushes and diarrhoea due to neuroendocrine tumours with an increasing incidence in seniors (25,26). They may be primary located in skin (which is rare) or specific dermatologic manifestations have been reported like type 1 neurofibromatosis (27,28). Moreover, serotonin via its receptors (type 3) sensitizes the cells from the level of the skin involving the response to irradiation (29).

DISCUSSION

We should also mention the skin effect of thyroid hormones knowing that thyroid conditions like nodules and some types of differentiated cancer has an increasing incidence during lifespan (30,31). The role of menopause is controversial in this topic but menopause also brings into the general picture of aging osteoporosis and a progressive increase of breast cancer prevalence and even ovarian carcinoma in elderly (32,33).

CONCLUSION

Skin is situated at the crossroad between intrinsic and extrinsic aging and the neuroendocrine approach is essential for understanding its time dependent changes.

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