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Review article

Local cortisol/corticosterone activation in skin physiology and pathology

Mika Terao*, Ichiro Katayama

Department of Dermatology, Osaka University Graduate School of Medicine, Suita, Japan

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ABSTRACT

Cortisol and corticosterone are the endogenous glucocorticoids (GCs) in humans and rodents, respectively. Systemic GC is released through the hypothalamic-pituitary-adrenal (HPA) axis in response to various stressors. Over the last decade, extra-adrenal production/activation of cortisol/corticosterone has been reported in many tissues. The enzyme that catalyzes the conversion of hormonally inactive cortisone/11-dehydrocorticosterone (11-DHC) into active cortisol/corticosterone in cells is 11β-hydroxysteroid dehydrogenase (11β-HSD). The 11β-HSD1 isoform is predominantly a reductase, which catalyzes nicotinamide adenine dinucleotide phosphate hydrogen-dependent conversion of cortisone/11-DHC to cortisol/corticosterone, and is widely expressed and present at the highest levels in the liver, lungs, adipose tissues, ovaries, and central nervous system. The 11β-HSD2 isoform, which catalyzes nicotinamide adenine dinucleotide$^+$-dependent inactivation of cortisol/corticosterone to cortisone/11-DHC, is highly expressed in distal nephrons, the colon, sweat glands, and the placenta. In healthy skin, 11β-HSD1 is expressed in the epidermis and in dermal fibroblasts. On the other hand, 11β-HSD2 is expressed in sweat glands but not in the epidermis. The role of 11β-HSD in skin physiology and pathology has been reported recently. In this review, we summarize the recently reported role of 11β-HSD in the skin, focusing on its function in cell proliferation, wound healing, inflammation, and aging.

Contents

1. Introduction

Cortisol and corticosterone are the endogenous glucocorticoids (GCs) in humans and rodents, respectively. The endogenous GC is

* Corresponding author.
E-mail address: mterao@derma.med.osaka-u.ac.jp (M. Terao).

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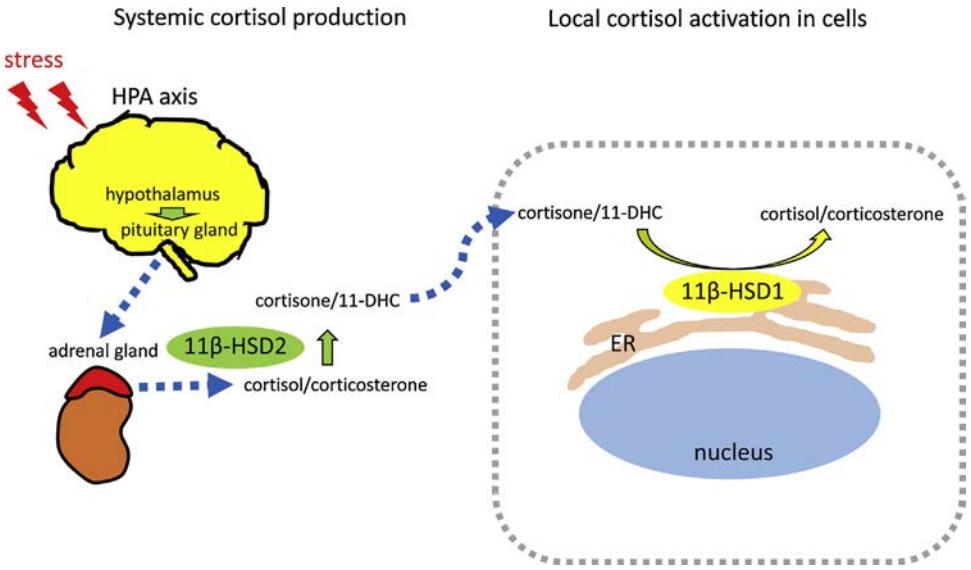

Fig. 1. Systemic cortisol production and local cortisol activation in cells. Abbreviations: 11β-HSD, 11β-hydroxysteroid dehydrogenase; ER, endoplasmic reticulum; HPA, hypothalamic-pituitary-adrenal.

released in response to various stressors, such as physical injury and psychological stress. It regulates biological processes including growth, development, metabolism, and behavior [1,2]. Systemic GC is released through the hypothalamic-pituitary-adrenal (HPA) axis. In response to stress, the hypothalamus secretes corticotropin-releasing hormone, which stimulates the release of adrenocorticotropic hormone from the pituitary and cortisol from the adrenal cortex.

In addition to the production of cortisol/corticosterone through the HPA axis, extra-adrenal production/activation of cortisol/corticosterone has been reported in tissues, such as the colon, heart, and lung [3–9] (Fig. 1). Skin is known to have neuroendocrine properties. Skin cells can produce hormones, such as thyroid stimulating hormone, oxytocin, growth hormone, thyroid-releasing hormone, and corticotropin-releasing hormone [10]. In addition, skin is steroidogenic tissue as it expresses CYP11A1, the enzyme that initiates conversion of cholesterol to pregnenolone. Production of cortisol in skin cells was first reported in melanoma cells, and then in melanocytes [11,12]. We and others reported local cortisol/corticosterone activation in the skin via the cortisol-activating enzyme 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1) [13].

Skin is exposed daily to various forms of mechanical and chemical stimulation. Chemical stimuli, such as ambient particulate matter, induces barrier disruption [14]. In addition, ultraviolet B (UVB) irradiation, tape stripping, and *Staphylococcus aureus* colonization are known to induce proinflammatory cytokines, such as tumor necrosis factor α and interleukin-6 [15,16]. Thus, we hypothesized that local cortisol/corticosterone activation by 11β-HSD1 in keratinocytes plays a role in regulating local stress to counterbalance repeated stimulation.

In this review, we summarize data recently reported on the role of cortisol/corticosterone-activating enzyme 11β-HSD in the skin, especially focusing on its function in cell proliferation, inflammation, and aging.

2. Local cortisol activation in the skin

11β-HSD catalyzes the interconversion between hormonally active cortisol/corticosterone and inactive cortisone/11-dehydrocorticosterone (11-DHC) in cells. The two isoenzymes of 11β-HSD both reside in the membrane of the endoplasmic reticulum [17]. The 11β-HSD1 isoform is predominantly a reductase, which catalyzes nicotinamide adenine dinucleotide phosphate hydrogen-dependent conversion of cortisone/11-DHC to cortisol/corticosterone, and is widely expressed and present at the highest levels in the liver, lungs, adipose tissues, ovaries, and central nervous system. In some cells, it also acts as a nicotinamide adenine dinucleotide phosphate-dependent dehydrogenase. The 11β-HSD2 isoform, which catalyzes nicotinamide adenine dinucleotide$^+$-dependent inactivation of cortisol/corticosterone to cortisone/11-DHC, is highly expressed in distal nephrons, the colon, sweat glands, and the placenta (Fig. 2). Approximately 90% of the released cortisol is bound to corticosteroid-binding protein. On the other hand, cortisol's inactive form, cortisone, has a lower binding affinity to corticosteroid-binding protein. Circulating cortisone is converted to active cortisol in tissue through 11β-HSD1.

Association of 11β-HSD1 with various diseases has been reported. In 2001, Masuzaki et al. reported that transgenic mice overexpressing 11β-HSD1 in adipose tissue had increased adipose levels of corticosterone and developed visceral obesity that was exacerbated by a high-fat diet [18]. Since then, other studies have reported that 11β-HSD1 is associated with obesity. 11β-HSD1 is also associated with other diseases, including rheumatoid arthritis, inflammatory bowel disease, polycystic ovary syndrome, and lung disease [9,19–22].

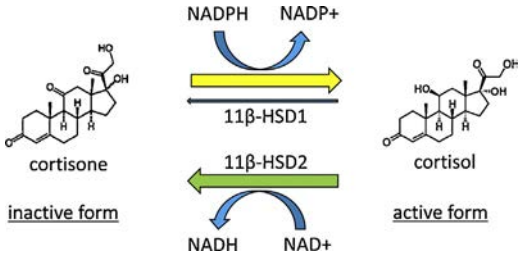

Fig. 2. A schematic of the reactions catalyzed by 11β-hydroxysteroid dehydrogenase (11β-HSD)-1 and −2. Abbreviations: NAD$^+$, nicotinamide adenine dinucleotide$^+$; NADH, nicotinamide adenine dinucleotide hydrogen; NADP$^+$, nicotinamide adenine dinucleotide phosphate$^+$; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen.