

## Evaluation of Serum Urocortin 3 in acne vulgaris patients

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### Abstract

**Background:** Acne vulgaris is a prevalent skin disorder characterized by various inflammatory lesions. The pathogenesis of acne involves complex interplays of multiple factors, including increased sebum production, inflammation, and immune responses. Urocortin 3 (UCN 3), a neuropeptide with diverse physiological functions, has been implicated in skin barrier function and immune modulation. However, its role in acne vulgaris remains poorly understood. **Objective:** This descriptive review aims to provide an overview of UCN 3, explore its known physiological functions, elucidate the pathogenesis of acne vulgaris, and discuss the multifactorial nature of acne development, considering genetic, environmental, and lifestyle factors. **Conclusions:** The reviewed literature indicates that Urocortin 3 (UCN 3) holds potential implications in acne pathogenesis, as evidenced by its presence in acne-affected skin and altered serum levels in acne patients. Its known physiological functions in stress regulation, inflammation, and immune responses suggest possible roles in acne development and severity. While specific mechanisms remain unclear, exploring UCN 3's interactions with known acne-related pathways may unveil novel therapeutic targets for acne management.

**Keywords:** Acne vulgaris; Urocortin 3; neuropeptide; serum levels; disease severity; biomarker; pathogenesis.

### 1. Introduction

Acne vulgaris, sometimes known as acne, is a widespread skin ailment that affects millions of people throughout the globe. It is characterised by the formation of comedones (blackheads and whiteheads), papules, pustules, and sometimes nodules and cysts [1].

Due to increased sebum production, follicular hyperkeratinisation, and colonisation of the hair follicles by the bacteria *Propionibacterium acnes*, acne typically arises throughout adolescence. Acne may affect a person's physical appearance, self-esteem, and quality of life even as an adult [2].

In recent years, interest in the involvement of neuropeptides in numerous physiological processes has increased. In the neural system, neuropeptides serve as neurotransmitters or neuromodulators. In addition to their conventional involvement in neuronal transmission, neuropeptides have been shown to have important roles in non-neuronal tissues and systems, such as the skin [3].

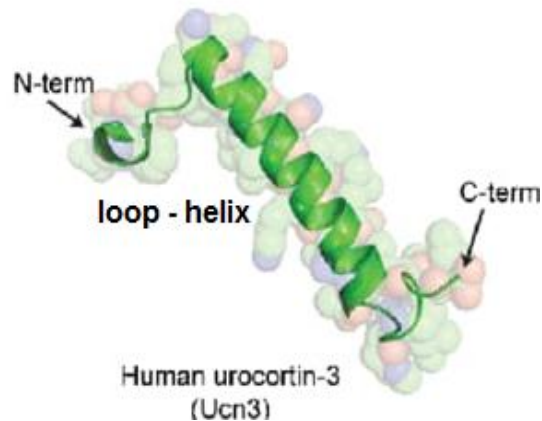
Intriguing neuropeptides include Urocortin 3 (UCN 3), a corticotropin-releasing factor (CRF) family member. UCN 3 was first discovered for its involvement in regulating the hypothalamic-pituitary-adrenal (HPA) axis and the stress response, but it has now been proven to influence a variety of other physiological processes. Recent studies have linked UCN 3 to the control of cardiovascular function,

energy balance, inflammation, and immunological responses [4].

The possible role of Urocortin 3 in the aetiology of acne has arisen as a topic of study. In light of the physiological roles of UCN 3 and its effect on inflammation and immunological responses, researchers suggest that this neuropeptide may be implicated in the complicated processes behind acne formation. Understanding the involvement of UCN 3 in acne may have major consequences for unravelling the pathophysiology of the disease and identifying potential treatment targets [5]. The aim of this review is to provide a comprehensive overview of the existing literature on the evaluation of serum Urocortin 3 in patients with acne vulgaris.

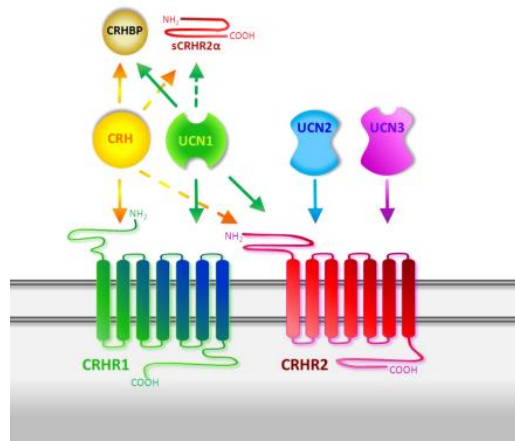
### 2. Urocortin 3 (UCN 3):

The peptide Urocortin 3 (UCN 3) is a member of the corticotropin-releasing hormone (CRH) family. It is one of three Urocortin variations, the others being UCN 1 and UCN 2. The anatomical distribution and activities of UCN 3, also known as stresscopin, are distinct from those of CRH, the principal member of the CRH family. UCNs, particularly UCN 3, are implicated in the recovery response to stress, while CRH is primarily responsible for initiating and regulating stress reactions through the hypothalamic-pituitary-adrenal (HPA) axis (Fig. (1) [6].



**Fig. (1)** Human UCN 3, originally named stresscopin to implicate its stress-coping activity, consists of a small N –terminal helix and a long C –terminal alpha helix containing 20 residues. This type of helix –loop –helix is critical for interactions with specific receptors. The links between the N- and C-terminal helices are thought to be crucial to ligand receptor interactions [4].

UCN 3 exerts its effect through attaching to the G-protein-coupled receptors CRHR1 and CRHR2. UCN 3 is a ligand selective for CRHR2. The activation of CRHR1 in the hypothalamus by CRH begins the HPA axis, resulting in the release of glucocorticoids (cortisol in primates and corticosterone in rodents) from the adrenal cortex. Activation of CRHR2 by UCNs, notably UCN 3, is essential for recovery from stress reactions and homeostasis restoration (**Fig. (2)**) [7].



**Fig. (2)** CRH-family members, their receptors and binding proteins. The arrows represent ligand-receptor or ligand-binding protein interactions. Dashed arrows indicate relatively low binding affinities, compared to unbroken arrow-lines. CRH displays a relatively high affinity for CRHR1 and low affinity for CRHR2. UCN1 binds to both receptors with equal affinity. UCN2 and UCN3 are selective ligands for CRHR2. CRHBP is able to sequester both CRH and UCN1. The same is also proposed for the recently discovered sCRHR2 $\alpha$ , but not yet proven. Abbreviations: corticotropin-releasing hormone (CRH), urocortin 1 (UCN1), urocortin 2 (UCN2), urocortin 3 (UCN3), CRH receptor 1 (CRHR1), CRH receptor 2 (CRHR2), CRH binding protein (CRHBP), soluble variant of CRHR2 (sCRHR2 $\alpha$ ) [6].

UCN 3 is involved in a variety of physiological activities, including as stress response, eating behaviour, energy balance, immunological responses, cardiovascular systems, inflammatory control, and reproduction. It is expressed in distinct areas of the central nervous system (CNS) and peripheral tissues, including the cardiovascular system, adipose tissue, skin, thyroid tissue, spleen, pancreas, kidney, skeletal muscles, gastrointestinal tract, and reproductive organs [8].

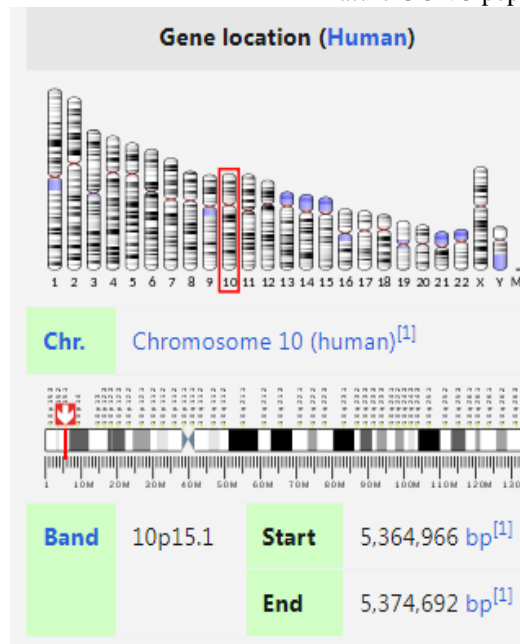
UCN 3 is present in the hypothalamus, medial amygdala, and limbic areas of the brain. It has been implicated in the regulation of the hypothalamic-pituitary-adrenocortical axis (HPA) and behaviour associated with anxiety and depression [9].

UCN 3 has been linked to a variety of diseases and may serve as a therapeutic target in some instances. Obesity, insulin secretion, itching, polycystic ovarian syndrome (PCOS), and renal cell cancer have been associated to it. In addition, UCN 3's potential therapeutic

benefits in disorders such as intracerebral haemorrhage, depression, forgetfulness, cardiovascular diseases, and alcohol consumption control have been examined [10].

**Structure, Synthesis, and Distribution in the Body:**

UCN 3 is a 38-amino acid peptide that is produced by the CRHR2 gene on human chromosome 7; it is a product of the CRHR2 gene. The gene generates a preproprotein that is processed post-translationally to generate the mature UCN 3 peptide (Fig. (3) [10].



**Fig. (3)** UCN 3 is a protein that in humans is encoded by the UCN 3 gene is located on chromosome 10p 15.1 <sup>[11]</sup>.

UCN 3 is a 38-amino acid peptide that is produced by the CRHR2 gene on human chromosome 7; it is a product of the CRHR2 gene. The gene generates a preproprotein that is processed post-translationally to generate the mature UCN 3 peptide [12].

In addition to the brain, UCN 3 has been detected in several peripheral tissues and organs. These include the skin, heart, digestive system, pancreatic islets, and adrenal glands. This extensive distribution implies that UCN 3 may have several roles in the body [12].

**Known Physiological Functions:**

Urocortin 3 (UCN 3) has a variety of physiological roles. As a member of the corticotropin-releasing factor (CRF) family, UCN 3 plays a crucial role in stress management by regulating the hypothalamic-pituitary-adrenal (HPA) axis, therefore causing the adrenal cortex to secrete glucocorticoids.

These glucocorticoids control immunological function and metabolism and coordinate the body's stress response. In addition, UCN 3 has been linked to cardiovascular control, including effects on heart rate, blood pressure, and cardiac contractility. It is also important in maintaining energy homeostasis, and its interactions with neuropeptides and neurotransmitters involved in appetite control may influence food intake. Emerging data also implicates UCN 3 with immunological regulation and inflammation, since it works on immune cells and influences cytokine production. UCN 3 influences reproductive hormones and behaviours, hence playing a role in reproductive function. The many actions of UCN 3 highlight its importance as a neuropeptide with vast effects throughout the body [13]. **Table 1**

**Table (1)** Overview of Known Physiological Functions of Urocortin 3 (UCN 3)

Physiological Function	
<b>Stress Regulation</b>	UCN 3 plays a key role in regulating the hypothalamic-pituitary-adrenal (HPA) axis, the central neuroendocrine system responsible for the body's response to stress. Upon HPA axis activation, UCN 3 is released from the hypothalamus and acts on the anterior pituitary to stimulate the release of adrenocorticotropic

<b>Cardiovascular Function</b>	<p>hormone (ACTH). This, in turn, leads to the secretion of glucocorticoids from the adrenal cortex. Glucocorticoids are vital for coordinating the body's stress response, including immune function and metabolism modulation.</p> <p>UCN 3 is implicated in regulating cardiovascular function. Studies suggest that UCN 3 influences heart rate, blood pressure, and cardiac contractility by acting on the heart and blood vessels. Additionally, UCN 3 may have protective effects on the cardiovascular system, particularly under conditions of stress or injury.</p>
<b>Energy Homeostasis</b>	<p>UCN 3 is linked to the regulation of energy balance and metabolism. It appears to be involved in controlling food intake and may play a role in maintaining energy homeostasis through interactions with other neuropeptides and neurotransmitters involved in appetite regulation.</p>
<b>Inflammation and Immune Responses</b>	<p>Emerging evidence suggests that UCN 3 may modulate immune responses and inflammation. UCN 3 receptors are present on immune cells, and UCN 3 administration has been shown to affect immune cell function and cytokine production.</p>
<b>Reproductive Function</b>	<p>UCN 3 is involved in regulating reproductive processes, including the control of reproductive hormones and behaviors. Its actions in the reproductive system may impact fertility, reproductive health, and mating behaviors.</p>
<b>Acne Vulgaris:</b>	<p>multifaceted, including hormonal factors, inflammation, sebum production, and hyperkeratinization of hair follicles [14].</p>
<p>Acne vulgaris is a common skin condition that typically affects adolescents but may linger into adulthood. Its pathophysiology is</p>	<p>paired with excess sebum and bacteria, grow to bigger comedones [18].</p>
<b>Pathophysiology of Acne Vulgaris:</b>	
<b>Hormonal Influences:</b>	<p><b>Multifactorial Nature of Acne Development:</b> Multiple factors contribute to the development of acne vulgaris, which is a complex disorder. These variables may be generically classified as genetic, environmental, and lifestyle variables [19]:</p>
<p>Androgens, a class of male sex hormones, play a vital role in the development of acne. There is an increase in testosterone production throughout adolescence, which encourages the skin's sebaceous glands to create more sebum. Sebum is an oily fluid that lubricates the skin, but its overproduction may cause pores to get blocked [15].</p>	<p><b>Genetic Factors:</b> The susceptibility of a person to acne is significantly influenced by genetic disposition. The probability of acquiring acne is increased by a family history of the disorder. Certain genetic variants may affect hormone balance, sebum production, and skin inflammation, all of which may contribute to the development of acne [20].</p>
<b>Inflammation</b>	<b>Environmental Factors:</b>
<p>Acne development relies heavily on inflammatory mechanisms. Sebum generated in excess mixes with dead skin cells to create a clog that obstructs the entrance of the hair follicle. This clog fosters the growth of the acne-causing bacteria <i>Propionibacterium acnes</i>, which is naturally present on the skin. The increased bacterial colonisation induces an immunological response, which results in inflammation and the production of red, painful, pus-filled acne lesions [16].</p>	<p>Environmental factors may worsen or initiate acne. Certain pollutants, allergens, and occupational variables (such as exposure to oils or chemicals) might exacerbate acne lesions. In addition, environmental variables may affect hormone levels and stress, both of which are associated with the aetiology of acne [21].</p>
<b>Sebum Production</b>	<b>Lifestyle Factors:</b>
<p>Androgens activate sebaceous glands to increase sebum production. Acne-prone people may have sebaceous glands that are hyperactive, resulting in an excess of sebum production. This increased production of sebum leads to the growth of comedones (blackheads and whiteheads) and inflammatory acne lesions [17].</p>	<p>Acne may be affected by a person's way of life. Foods with a high glycemic index and dairy products are possible acne aggravators that may be influenced by diet. Inadequate dietary practises may also result in insulin resistance, which may aggravate acne. In addition, stress and lack sleep may cause hormonal shifts and inflammation, which contribute to acne outbreaks [22].</p>
<b>Follicular Hyperkeratinization:</b>	<p><b>Mechanisms of UCN 3 in Acne Pathogenesis Modulation of Sebum Production:</b></p>

Sebum production is one of the most important components in acne development. It has been found that UCN 3 regulates skin lipid metabolism and sebaceous gland activity. It is conceivable that UCN 3 interacts with sebocytes, the cells responsible for sebum production, to modulate sebum secretion. Dysregulation of UCN 3 signalling may contribute to the creation of comedones by causing an increase in sebum production (blackheads and whiteheads) [23].

#### **Inflammatory Modulation:**

It is known that UCN 3 has immunomodulatory effects, and its presence in immune cells has been established. Inflammation caused by the immunological response to *Propionibacterium acnes* inside blocked hair follicles characterises acne. UCN 3 may regulate the immunological response in the skin, hence influencing the severity of inflammation and the consequent production of acne lesions [24].

#### **Regulation of Hair Follicle Keratinization:**

It is known that UCN 3 has immunomodulatory effects, and its presence in immune cells has been established. Inflammation caused by the immunological response to *Propionibacterium acnes* inside blocked hair follicles characterises acne. UCN 3 may regulate the immunological response in the skin, hence influencing the severity of inflammation and the consequent production of acne lesions [25].

#### **Interaction with Neurotransmitter Systems:**

The neuropeptide UCN 3 interacts with several neurotransmitter systems. Dopamine and serotonin neurotransmitters have been linked to acne aetiology. It is likely that UCN 3 might have an effect on these neurotransmitter systems, hence affecting the development of acne [26].

#### **Hormonal Regulation:**

Androgens have an important part in the development of acne. UCN 3 may interact with the hormonal systems involved in sebum production and inflammation, altering the skin's equilibrium of androgenic and anti-androgenic signals [27].

#### **Influence on Stress Response:**

It is recognised that stress may aggravate acne in some persons. UCN 3 is implicated in the control of stress, and chronic stress may lead to dysregulation of UCN 3 signalling, which may influence the severity of acne via stress-induced hormonal and immunological alterations [28].

#### **Vascular Effects:**

UCN 3 has been linked to cardiovascular function and control. As acne lesions are often characterised by redness and vascular

abnormalities, UCN 3 may have some effect on the vasculature and redness of acne lesions that are inflamed [29].

#### **Clinical Implications and Future Perspectives:**

Due to UCN 3's multiple roles, including control of stress, inflammation, and immunological modulation, the link between Urocortin 3 (UCN 3) and acne vulgaris has intriguing therapeutic importance. Understanding the involvement of UCN 3 in acne pathogenesis may provide light on the processes behind the development and severity of acne. Exploring the association between serum UCN 3 levels and acne severity may have diagnostic and therapeutic consequences, providing as a possible diagnostic marker and target for innovative acne therapies. Strategies for stress management and immunomodulation might complement standard acne treatments. To realise its full therapeutic potential for acne treatment, however, further study is required to understand UCN 3's specific processes in acne, association with acne subtypes, and results in longitudinal studies and clinical trials [30].

#### **3. Conclusions:**

In conclusion, the reviewed literature indicates that Urocortin 3 (UCN 3) holds potential implications in acne pathogenesis, as evidenced by its presence in acne-affected skin and altered serum levels in acne patients. Its known physiological functions in stress regulation, inflammation, and immune responses suggest possible roles in acne development and severity. While specific mechanisms remain unclear, exploring UCN 3's interactions with known acne-related pathways may unveil novel therapeutic targets for acne management.

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