The Multiple Roles of Urocanic Acid in Health and Disease

Prue H. Hart¹ and Mary Norval²

Trans-urocanic acid (trans-UCA) is synthesized in the skin, liver, and brain. It is a major natural moisturizing factor in skin and maintains its acid pH. In skin, it isomerizes to cis-UCA following exposure to UVR. Both isomers fulfill multiple roles in health and disease. cis-UCA has immunomodulatory properties linked with several cutaneous diseases such as skin cancer, atopic dermatitis, and urticaria and associates with systemic diseases including multiple sclerosis. The levels of UCA in the skin, brain, urine, and feces reflect some physiological processes and may be disease biomarkers. Both isomers of UCA have therapeutic potential for a range of disorders.

Introduction

Urocanic acid (UCA) was first discovered more than a hundred years ago in the urine of a dog, hence, the name (Jaffe, 1874). It is located mainly in the uppermost layers of human skin, particularly in the stratum corneum, where it constitutes approximately 0.7% of the dry weight of the epidermis (Tabachnick, 1957). The acid pH found in the stratum corneum, which is essential for the optimal function of several enzymes and antimicrobial defenses, is due to UCA (Krien and Kermici, 2000) together with other factors, including free fatty acids and sodium-hydrogen exchanger-1 activation (Proksch, 2018). The concentration of UCA in skin varies considerably between individuals, from around 4 nM per cm² to 34 nM per cm², and within an individual, there is little difference in concentration at sun-exposed and unexposed body sites (Kavanagh et al., 1995). The amount does not correlate with age, sex, pigmentation, photosensitivity, minimal erythema dose, and stratum corneum thickness (de Fine Olivarius et al., 1996a). Proteins rich in histidine, predominantly FLG, which contains 10% histidine residues, break down into smaller peptides and amino acids as the keratinocytes (KCs) in the epidermis become terminally differentiated. Histidase (L-histidine ammonia lyase) is activated in this site with the subsequent formation of UCA from histidine. UCA accumulates as the enzyme that catalyzes it, urocanase, is not present in skin. UCA is also found in the liver and recently in the brain (Zhu et al., 2018) where, in contrast to skin, urocanase is located which catalyzes UCA to imidazolone-propionic acid, with further breakdown to glutamic acid (GLU).

UCA absorbs UVR and, in doing so, isomerizes from the naturally occurring trans form to cis-UCA until an equilibrium is reached on continued exposure to UVR with a maximum of around 60% cis-UCA. Following irradiation, cis-UCA is found in serum (Moodycliffe et al., 1993) and is excreted in urine for up to 12 days (Kammeyer et al., 1997). The action spectrum for the production of cis-UCA is most effective within the UVB waveband at 280–310 nm in human skin (McCloone et al., 2005). Because of the relative abundance of UCA in human skin and its ability to absorb UVR, it was initially proposed to act as a natural sunscreen to protect against sunburn and damage to cutaneous DNA (reviewed in Morrison [1985]). This was confirmed subsequently (Barresi et al., 2011; Bruhs et al., 2016), although its sun protection factor is estimated as only 1.5 (de Fine Olivarius et al., 1996). Furthermore, the in vitro action spectrum for singlet oxygen generation after excitation of trans-UCA mimics the in vivo action spectrum for photoaging of skin, showing that UCA plays a role in photoaging through UVA sensitization (Hanson and Simon, 1998; Shen and Ji, 2008).

Cis-UCA is now recognized to act in a more complex manner than purely as a chemical sunscreen. In a landmark publication, De Fabo and Noonan (1983) hypothesized that cis-UCA could act as a cutaneous photoreceptor for UVR-induced suppression of cell-mediated responses. Supporting evidence was rapidly obtained, which was reviewed in Gibbs et al. (2008) and Norval et al. (1995). More recently it has become clear that cis-UCA has several mechanisms of action and that it is involved in mediating a wide range of clinical effects. Many studies have aimed to identify the receptor to which cis-UCA binds and its consequent downstream signaling. However, as shown in Table 1, several receptors have been found, leading to the possibility that it may vary with cell type. In addition, because of the chemical properties of UCA and its position in the histidine to GLU metabolic pathway, novel clinical aspects are becoming apparent.

In this review, the evidence to date linking cis-UCA, both UVR-induced and synthetically produced, as immunomodulatory molecules in skin and systemic diseases is outlined. In some cases, the levels of UCA per se are determinants of disease and physiological processes; the quantity of UCA

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Abbreviations: AD, atopic dermatitis; GLU, glutamic acid; KC, keratinocyte; MC, mast cell; UCA, urocanic acid

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<td>Arentsen et al. (2012); Lahia et al. (2010, 2009); Peuhu et al. (2010)</td>
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(continued)
may also be an important biomarker of disease pathways. Both UCA and cis-UCA have been investigated as therapeutic agents. All these aspects are briefly considered.

**Involvement of cis-UCA in skin**

**Skin cancer.** Since the mid-1980s, the traditional view has been that cis-UCA induces immunosuppression, which is likely to contribute to a diminution in controlling tumorigenesis. In addition, cis-UCA initiates oxidative DNA damage and induces genes in cultured human KCs associated with apoptosis, cell growth arrest, and oxidative stress (Table 1) (Kaneko et al., 2011, 2009, 2008; Sreevidya et al., 2010). Beissert et al. (1997) demonstrated that the presentation of tumor antigens in vitro by Langerhans cells was inhibited by cis-UCA. Furthermore, a reduced incidence of skin tumors was found in chronically UVB-irradiated mice that were treated throughout the exposures with a cis-UCA–specific mAb compared with unirradiated mice (Beissert et al., 2001). Finally, limited studies in humans demonstrated a higher level of cis-UCA in biopsies of squamous cell carcinoma than in skin from the periphery of the tumor (Decara et al., 2008), and although no difference was found in UCA concentration or percentage of cis-UCA in several skin sites in patients with previous basal cell carcinomas or cutaneous malignant melanomas compared with healthy controls, the relative production of cis-UCA was higher in both patient groups following irradiation with a single UVB dose (de Fine Olivarius et al., 1998b).

An additional property of cis-UCA relates to the treatment of skin cancer rather than to its role in skin cancer. The extracellular tumor microenvironment is acidified, which boosts invasiveness and metastasis, whereas the intracellular pH of the tumor and stromal cells is neutral. Cis-UCA can acidify the cytosol of tumor cells by transporting protons intracellularly (termed the photodynamic concept), a process that leads to the activation of an apoptotic signaling cascade and cell death (Table 1) (Laihia et al., 2009). Laihia et al. (2010) demonstrated that the growth of human melanoma xenografts in immunodeficient mice was suppressed by 60% following intratumoral injections of cis-UCA three times weekly for 2 weeks. By a similar photodynamic process, cis-UCA stimulated apoptotic and necrotic cell death of human bladder carcinoma cells in vitro (Peuhu et al., 2010). In an orthotopic rat urothelial carcinoma model, cis-UCA administered intravesically on three occasions reduced the percentage of tumors that were muscle invasive from 100% to 43% at 12 days after tumor cells were instilled into the acid-treated bladder (Arentsen et al., 2012).

In summary, UV-induced cis-UCA promotes skin cancer by reducing cell-mediated immunity. Its ability to acidify the cytosol of tumor cells may lead to its use in the local treatment of selected cancers.

**Other skin diseases.** Cis-UCA can reduce both acute and subacute skin inflammation (Laihia et al., 2012). In mouse models, cis-UCA, at a mild acidic pH, applied topically was more effective than hydrocortisone or tacrolimus in decreasing skin irritation, edema, and erythema. It did not affect the infiltration of neutrophils into the skin or reduce the thickness of the epidermis but was proposed to act by decreasing the local activity of the neutrophils.

In patients with chronic spontaneous urticaria (transient wheals and/or angioedema), there was a higher concentration of cis-UCA in the stratum corneum and an increase in the cis-UCA-to-trans-UCA ratio compared with healthy controls (Pham et al., 2017). As cis-UCA but not trans-UCA enhances IgE-mediated basophil activation and the IgE- and calcium-mediated degranulation of cultured human mast cells (MCs), the increased ratio could lead to the enhancement of MC degranulation and thus promote the symptoms of urticaria. This conclusion was supported by evidence indicating that cis-UCA can induce degranulation of MCs in skin (Wille et al., 1999), possibly via stimulation of neuropeptide release from sensory nerves (Khalil et al., 2001).

It is recognized that loss of function mutations in the FLG gene constitute the strongest known risk factor for atopic dermatitis (AD) in Northern European and Asian populations (Sandilands et al., 2009). These result in a reduction or complete absence of epidermal FLG. However, in most patients with AD, FLG is wild-type, but epigenetic effects, including compromised pro-FLG processing, lead to reduced levels of natural moisture factor amino acids, including histidine and UCA (Kezic et al., 2011). Thus, impaired barrier integrity and skin hydration result (Panther and Jacob, 2015). In addition, there is lack of control of infiltrating neutrophils (Laihia et al., 2012), and other proinflammatory cells. Increased levels of sphingosine, sphinganine, and their ceramides in atopic skin also contribute to skin barrier dysfunction and correlate with disease severity and increased cytokine levels (Toncic et al., 2020).

These findings point to the possibility of using UCA directly in local therapy of AD. Peltonen et al. (2014) treated patients...
with AD who had chronic mild-to-moderate disease with 5% cis-UCA emulsion cream on selected skin lesions twice daily for 28 days. The cream was well tolerated with no systemic accumulation of cis-UCA. It led to reduced transepidermal water loss, reduced cutaneous erythema, and an improvement in the eczema area severity index although, disappointingly, the latter was not significant, perhaps because of the short treatment period and the small lesions studied. An allied approach has been taken by Tan et al. (2017) in which, first, the addition of L-histidine to an in vitro human skin equivalent model caused an increase in FLG production and an improvement in skin barrier function. This strategy was then applied to patients with AD who ingested a supplement of L-histidine daily, which resulted in a 40% reduction in AD severity after 4 weeks. This effect was similar to that found with mid-potency topical steroids.

The loss-of-function genetic mutations in FLG that lead to a reduced production of epidermal trans-UCA might have evolved as humans migrated out of Africa with progressive skin lightening (Thyssen et al., 2014). This would result in less filtering of UVR in the skin and thus allow a more effective synthesis of previtamin D from 7-dehydrocholesterol on exposure to the sun. This view is strengthened by the discovery that the level of epidermal trans-UCA in an individual correlates inversely with the increase in vitamin D status (determined by serum 25-hydroxyvitamin D concentration) induced by suberythemal exposure to UVR (Landeck et al., 2016).

In brief, UCA isomers play a role in the control of skin inflammation in general and in specific cutaneous disorders, such as AD. Altering their concentration in the diseased skin may provide therapeutic benefits.

**Involvement of UCA in systems beyond the skin**

**UCA produced in UV-irradiated skin.** The systemic effects of UVR-induced UCA have been diverse; three examples are described hereafter.

Sleijffers et al. (2001) investigated immune responses following UV irradiation of volunteers before intramuscular vaccination with hepatitis B surface antigen. No alteration in protective T-cell or B-cell responses to the vaccine was found compared with unirradiated controls. However, volunteers with a higher content of cis-UCA in their skin following the UVR exposure had reduced vaccine-specific T-cell responses without a similar effect on their antibody responses (Sleijffers et al., 2003). These results in a human cohort support the potential of UVR-induced cis-UCA to modulate systemic immune responses in at least a subset of individuals.

The latitude gradient for most autoimmune diseases, including multiple sclerosis (higher latitude, less sun, disease more prevalent), supports UVR as an environmental regulator of autoimmune processes associated with these conditions (reviewed in Hart et al. [2017]). Correale and Farez (2013) found reduced cis-UCA levels in the plasma of patients with relapsing remitting multiple sclerosis compared with healthy controls, which may contribute to disease modulation by sunlight. Furthermore, they showed that cis-UCA incubated with PBMCs could increase the percentage of regulatory T cells and reduce antigen presentation by dendritic cells (Table 1). Further studies of the involvement of UCA in autoimmune diseases are of interest.

UCA has been detected in individual neurons in most areas of the brain of mice (Zhu et al., 2018). Following skin exposure to UVR, its concentration was increased in the blood first and then, after 2 hours, at all sites in the brain except the nucleus accumbens. The increase in UCA returned to baseline by 24 hours. Intravenous injection of UCA instead of UVR exposure led to the same changes in the brain. Use of 13C-labeled histidine allowed detection and quantification in single neurons of components of the histidine to GLU pathway with UCA as one of the intermediates. Also, the enzymes required in the histidine-UCA-GLU pathway, including histidase, urocanase, and imidazolonepropionase, are present in many regions of the brain. The addition of 13C1,-UCA to hippocampus neurons led to higher levels of 13C2,-GLU, confirming a pathway of increased flux with increased UCA input. GLU is an important excitatory neurotransmitter in the vertebrate nervous system. Electrophysiological recording of brain slices demonstrated enhanced glutamatergic synaptic transmission following UVB exposure, and this is associated with improved motor learning and recognition and long-term memory. Thus, there is a novel GLU biosynthetic pathway in neurons; histidine is metabolized to UCA and then GLU. With increased UCA after UVB exposure, more GLU is available for packaging into synaptic vesicles and their release from nerve terminals, with positive effects on memory and learning. The importance of this UVB-enhanced, GLU-producing pathway is suggested by the inverse association between learning disabilities and low maternal exposure to UVB (as estimated by total sunshine hours and antenatal UVB and/or UVA radiation exposure) in a population cohort study of 422,512 children in Scotland (Hastie et al., 2019).

**Potential of synthetically produced cis-UCA to modulate systemic diseases.** Investigations in animal models have demonstrated the potential of cis-UCA to modulate inflammatory diseases of the bowel, eye, and bladder. Daily subcutaneous injections of cis-UCA (50 µg per mouse) reduced chemical-induced intestinal inflammation in mice by a process dependent on IL-10 (Albert et al., 2010). cis-UCA also stimulated anti-inflammatory and cytoprotective effects on UVB-irradiated human corneal and human conjunctival epithelial cells in vitro (Table 1; Jauhonen et al., 2011; Viiri et al., 2009). In subsequent studies, cis-UCA added to eye drops at 2.5% was safe and well tolerated in healthy individuals (Jauhonen et al., 2015). In addition, it could prevent ocular surface irritation in two rat models (Jauhonen et al., 2017). The first involved IgE-independent ocular inflammation induced by C48/80 application where cis-UCA was as effective as the known regulatory agents ketotifen and dexamethasone. The second was an ovalbumin-induced ocular allergy model in which cis-UCA, like olopatadine, could significantly inhibit conjunctival vascular leakage. For treatment of acute hydrochloride acid–induced bladder inflammation, 2% cis-UCA as an intravesical infusion was as efficient as a proven treatment, 0.5% hyaluronic acid, in improving bladder function in rats (Konkol et al., 2016). Histopathological studies suggested that the anti-
inflammatory actions of cis-UCA were due to its tissue-protective properties in reducing the detrimental activity of acute phase immune cells already present in the bladder, without affecting the infiltration of inflammatory cells.

In summary, cis-UCA may control inflammation in multiple tissues.

**UCA as part of a nonviral complex for gene therapy.** The chemical properties of UCA may enhance the efficacy of gene therapy. Chitosan is a natural cationic polymer that can condense effectively with negatively charged DNA via electrostatic interaction. The coupling with 10–30% UCA significantly improves solubility at physiological pH, and the high amine content in UCA increases nucleic acid binding and condensation (Hsueh et al., 2017). Studies suggest that the complexes enter the endosomes and/or lysosomes of cells by a clathrin-dependent pathway in which UCA improves buffering capacity by a proton sponge effect. Protons and chloride accumulate in the endosomes and, together with secondary water influx, the endosome membranes are destabilized and rupture (Kim et al., 2003). In further developments (Guo et al., 2014; Han et al., 2015; Xiao et al., 2016), UCA has been linked with cationic polymers to enhance DNA, small interfering RNA, and drug delivery into the cytoplasm of cells without any demonstrable cytotoxicity. The pH sensitivity of the nanoparticles, principally because of the UCA molecules, has been central to the success of the chitosan (or similar)-UCA-payload complexes. The significance of these complexes is enhanced as they are non-immunogenic, unlike nucleic acid–carrying viral vectors.

**UCA levels in skin, urine, and fecal samples as a metabolic biomarker of diverse diseases**

Several examples of the association between UCA levels in the metabolome of skin, urine, and feces and various diseases follow. In the skin metabolome of patients with psoriasis, UCA concentration correlated negatively with plaque severity scores, and the amount in excretions from psoriatic lesions was approximately half of that from healthy skin (Dutkiewicz et al., 2016). Similarly, reduced levels of UCA, compared with age-matched controls, were present in the urine of atopic asthmatic children, which did not correlate with the patients’ prescribed drugs (Mattarucchi et al., 2012). Although a good biomarker, the metabolic or immune significance of this finding is not clear. The lower levels of UCA could be an indicator of reduced histidine metabolism, or, as cis-UCA is immunosuppressive, indicate the potential for increased inflammation. Likewise, when the urine of patients with endometrial carcinoma was examined for diagnostic biomarkers by ultra-high performance liquid chromatography–quadrupole time-of-flight mass spectrometry, the level of UCA was increased compared with healthy controls and was one of five biomarkers identified (Shao et al., 2016). The higher level may be due to a histidine or GLU metabolism disorder, and further research relating to UCA may contribute to the understanding of this cancer. UCA is significantly reduced in the feces from aged compared with young rats; Hor et al. (2019) proposed that, with age, there was a decline in skeletal muscle mass, less protein need, reduced amino acid metabolism, and, as a consequence, lower levels of UCA. Other than high levels of fecal UCA being a marker of youth, the functional role of UCA in the gut is unknown currently.

**Conclusions**

Depending on the body site, UCA may be pathogenic, beneficial, or useful as a marker of flux through biochemical pathways. The proven immunosuppressive properties of the cis-isomer, both locally in the skin and systemically, are critical in a number of disorders; it may be pathogenic for skin cancer development but helpful in autoimmune conditions. Also, the ability of cis-UCA to acidify the cytosol of tumor cells, and potentially of additional cell types, by transporting protons intracellularly and initiating apoptosis may be beneficial. Furthermore, UCA in skin and other tissues can be an important intermediary in the histidine to GLU metabolic pathway. In the brain, this is associated with increased excitatory neurotransmission; in other illnesses, the functional role of UCA is less clear, although the level may be a biomarker of the disease. The potential of UCA and cis-UCA as therapeutic agents has been demonstrated in several clinical studies, and the use of UCA to enhance gene therapy or intracellular drug delivery provides a further beneficial medical application.

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**CONFLICT OF INTEREST**

The authors state no conflicts of interest.

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**AUTHOR CONTRIBUTIONS**

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