INTRODUCTION

Urea is a naturally occurring humectant agent that is part of the water-soluble fraction of the stratum corneum. It can both retard and promote penetration into the skin. Enhancement of skin barrier function has been frequently reported and thus urea is widely used to improve dryness of the skin. In many skin diseases characterised by dryness such as atopic eczema and hand eczema, urea can delay relapses in these highly chronic conditions. With this in mind, urea has been used as a well-established ingredient in various topical applications for skincare and different skin diseases. However, many aspects of its mode of action are only partly understood. Most traditional publications focus on biophysical properties such as moisturising and keratolysis. The structural background of skin barrier implies that filaggrin which is part of the natural moisturising factor of the stratum corneum forming the cornified envelope of the corneocytes. Mutations in the filaggrin gene are characteristic observations in individuals with dry skin and demonstrate features of inflammatory skin conditions as atopic eczema. Strengthening impaired skin barrier function by the use of moisturisers can counteract dry skin and reduce the prevalence of inflammatory skin diseases, especially in individuals featuring mutations in the filaggrin gene. More recently, it has been described that urea exerts specific gene regulatory activities affecting mRNA expression of certain genes that play a role in the differentiation of keratinocytes. Improvement of skin barrier function has been known for decades as a characteristic of urea and results from this genetic modification of keratinocyte function. Thus, urea is not only an old-fashioned, but also physically acting molecule with simple, easy to understand mode of action. Beyond what we already know, it can become part of a physically induced molecular biology network to not only promote skincare but also lead the mechanisms of cure in various diseased skin conditions.

CLINICAL USE OF UREA

High concentrations of urea (20%-40%) are used to dissolve atrophic nails or destroyed nails in tinea unguium. In hyperkeratotic feet, urea can improve the situation at concentrations of 10%-40%. Furthermore, urea (10%) can reduce the thickness of the stratum corneum by reducing the number of stratum corneum cell layers. This effect is used to improve hyperkeratotic skin conditions as ichthyosis. Urea also improves the water-holding capacity of the skin which becomes clinically useful in ichthyotic skin. In psoriasis, urea (10%) can reduce plaque thickness but does not show effects on erythema, thus is not directly anti-inflammatory in this condition.

At concentrations of 4%-10%, urea could demonstrate beneficial effects on atopic dry skin and atopic eczema. Besides clinical improvement, effects on biophysical features of the skin could be shown as increased hydration and reduction in transepidermal water loss. Radio-induced dermatitis is a frequent adverse event in radiotherapy. Urea has been demonstrated to reduce the risk of radiodermatitis in patients with breast cancer.
Reports on effects of urea on penetration properties of the skin are controversial: some authors report promotion of absorption of different drugs as topical corticosteroids. However, other trials report an unchanged latency time to induce erythema after a 3-week treatment with a 3% urea-containing moisturiser.

3 | MODE OF ACTION

Physical properties of urea such as detachment of nails are because of its ability to unfold proteins, thus destroying them. Urea can also replace water and increase the resistance of the stratum corneum against osmotic stress. Interestingly, thymidine incorporation into DNA was observed after short-term contact with a saturated urea solution. Moreover, an altered expression of involucrin and cytokeratins has been reported in psoriatic patients indicating a reduction in epidermal DNA synthesis and proliferation. Decreased involucrin has also been observed in atopic subjects.

More recently, effects of urea beyond the physical ability to be part of the natural moisturising factor have been reported throwing light on new aspects of action. It seems that urea can stimulate epidermal differentiation and lipid synthesis and induce the synthesis of antimicrobial peptides in the epidermis as part of the skin’s immune system. Various findings support the ability of urea to take effect on gene transcription: human keratinocytes react on stimulation with physiological doses of urea in millimolar range by expression of transglutaminase 1, involucrin, filaggrin and loricrin. All these gene products are important players in keratinocyte differentiation and formation of antimicrobial peptides (eg, beta-defensin-2 and LL-37 precursor cathelicidin). The upregulation of enzymes involved in sphingolipid metabolism such as sphingomyelinase 1, involucrin, filaggrin and loricrin. All these gene products are important players in keratinocyte differentiation and formation of antimicrobial peptides (eg, beta-defensin-2 and LL-37 precursor cathelicidin).

The upregulation of enzymes involved in sphingolipid metabolism such as sphingomyelinase have also been observed. These effects could also be achieved if human skin was treated topically. Skin physiology measurements of transepidermal water loss that showed diminished values after a 20% urea treatment are the clinical link to this. It could be assumed that these effects result from urea-induced osmotic stress and thus are not specific. However, specific urea transporters have been identified. Urea is taken up by a specific mechanism involving two different urea transporters, which are upregulated by uptake of urea. Furthermore, urea can also be transported by aquaglyceroporins.

4 | SIDE EFFECTS

Urea is generally regarded as a safe topical agent as it represents a physiological agent. Cutaneous sensitisations have never been reported. Up to a concentration of 10%, urea topical creams do not induce inflammation or skin barrier disruption which becomes possible at higher concentrations. Redness and stinging, however, can be individual side effects especially encountered in children and at sensitive areas of the skin. It has been assumed that urea can take effect on cutaneous arterial sympathetic nerve activity and leads to elevated blood flow induced by histaminergic $H_3$ receptors.

5 | CONCLUSION

Urea has a large variety of properties: it is proteolytic, keratolytic, hydrating, hygroscopic, penetration-enhancing, and antipruritic. Without doubt, the moisturising action of urea in dry and atopic skin plays the most important role for skin care and treatment of various skin diseases, for example atopic eczema, ichthyosis, psoriasis. Reduction in epidermal proliferation and increase in differentiation are well-established properties of urea, on the skin. Beyond many mechanistic explanations of effects of urea more recently, it has been demonstrated that specific urea transporters coordinate urea uptake. Effects on gene transcription result in increased lipid synthesis and upregulation of antimicrobial peptides which play an important role in maintenance of healthy skin or improvement of structural and inflammatory skin diseases. Gene regulatory activities leading to restoration of skin barrier function and increased immune defence are decisive qualities for the treatment of atopic skin in particular.

Given these properties, it must be stressed that signal pathways triggered by urea are not fully understood. Further efforts must be taken to better understand the mechanisms of action of urea and possibly find new applications of this interesting agent.

DISCLOSURES

None to declare.

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