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Urea – new insights into a well-known active ingredient for dry skin

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Urea is an endogenous metabolite, known to enhance stratum corneum hydration. Yet, topical urea anecdotally also improves permeability barrier function, and it appears to exhibit antimicrobial activity. Hence, we hypothesized that urea is not merely a passive metabolite, but a small-molecule regulator of epidermal structure and function. In 21 human volunteers, topical urea improved barrier function in parallel with enhanced antimicrobial peptide (LL-37 and ß-defensin-2) expression. Urea both stimulates expression of, and is transported into keratinocytes by two transporters, UT-A1 and UT-A2, and aquaporin. Inhibitors of these urea transporters block the downstream biological effects of urea, which include increased mRNA and protein levels for: (i) transglutaminase-1, involucrin, loricrin and filaggrin; (ii) epidermal lipid synthetic enzymes, and (iii) cathelicidin and ß-defensin-2. Finally, we explored the potential clinical utility of urea, showing that topical urea applications normalized both barrier function and antimicrobial peptide expression in a murine model of atopic dermatitis (AD). Together, these results show that urea is a small-molecule regulator of epidermal permeability barrier function and antimicrobial peptide expression after transporter uptake, followed by gene regulatory activity in normal epidermis, with potential therapeutic applications in diseased skin.