Increased glucocorticoid hormone actions induce skin-specific Na\(^{+}\) and water loss in melanocortin 3 receptor knockout mice

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**Backgrounds:** We recently reported that the body differentially controls its body fluid content by natriuretic-ureotelic regulation, which is characterized by a balance between aldosterone/Na\(^{+}\)-driven or glucocorticoid/urea-driven water reabsorption in the biological barriers. We hypothesized that mice with elevated glucocorticoids shift this balance in favor of urea-driven water conservation and show decreased Na\(^{+}\) storage in the body.

**Methods:** We fed melanocortin-3-receptor (MC3R) knockout (KO) mice, which have elevated glucocorticoid levels, and wild-type (WT) control mice a low-salt diet (0.1% NaCl plus tap water) for 4 weeks. We studied 24-h osmolyte excretion and concentration in urine. We also measured body composition, tissue osmoles and water content, glucocorticoid-receptor (GR) protein/chromatin interaction, and arginase activity for urea production.

**Results:** MC3R-KO mice showed increased GR chromatin binding in skeletal muscle with reduced muscle mass and increased fat content, confirming endogenous glucocorticoid excess. MC3R-KO mice increased urea transporter (UT) A1 protein and urea content in the renal medulla, which was coupled with reduced urinary urea excretion and lower urine volume, while urinary Na\(^{+}\) excretion and urine osmolyte concentrations were similar to WT mice. MC3R-KO mice also showed increased arginase activity in skeletal muscle, but not in liver, kidney, or skin. Total body Na\(^{+}\) and water content were decreased in MC3R-KO mice because of reduced skin Na\(^{+}\) and water content. These skin-specific Na\(^{+}\) and water reductions were associated with high lymphatic vessel endothelial hyaluronan receptor-1 mRNA levels in the skin, suggesting that expanded cutaneous lymph vessels enhanced lymphatic osmolyte and water clearance in MC3R-KO mice. In line with our hypothesis, MC3R-KO mice increased skin urea content and reduced cutaneous Na\(^{+}\) content. This skin Na\(^{+}\) loss was not compensated by skin urea accumulation, resulting in reduced skin osmolyte content and cutaneous water loss.

**Conclusions:** Our findings confirm that fluid homeostasis is maintained by natriuretic-ureotelic regulation in kidney and skin. In MC3R-KO with central hypercortisolism, medullary urea osmolyte accumulation allows efficient renal water conservation. However, in the skin barrier, increased urea-driven water conservation is not sufficient to compensate for reduced skin Na\(^{+}\) accumulation, resulting in skin-specific water loss that reduces total body water content.