Protein kinase C-α comes to the rescue of aquaporin-2

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The article by Thai et al. (12) in an issue of the American Journal of Physiology-Renal Physiology brings to the forefront a previously unrecognized role of PKC-α in preventing down-regulation of aquaporin (AQP2) by ANG II.

Regulated transport of water, sodium, and urea in the renal medulla is crucial for maintaining a hyperosmolar interstitium to excrete concentrated urine while at the same time adequately retaining water. The main inner medullary water and urea transporters involved in this process are AQP2 and two urea transporters (UTs), UT-A1 and UT-A3, whose abundance and activity play a critical role in water balance. Regulation of these transporters is complex and involves crosstalk among many different factors affecting the urine concentration process.

More investigation in this area is necessary to elucidate the individual signaling pathways that confer the regulatory specificity of water and urea transport in distinct settings, and, in this respect, the study by Thai et al. represents a step forward.

Among the main factors controlling water and urea transport, ANG II and arginine vasopressin (AVP) have synergistic effects.

ANG II also induces AQP2 gene expression and protein abundance and stimulates its targeting to the apical membrane (8). The exchange protein activated by cAMP (Epac) may be implicated in the long-term control of AQP2 (7).

Short-term activation of AQP2 by vasopressin and PKA occurs by phosphorylation at Ser256 with mobilization of AQP2 to the apical membrane. Bioinformatic analysis and some in vitro studies have suggested that other kinases, such as PKG, may participate in AQP2 phosphorylation at different consensus sites (9).

Long-term expression of UT-A1 and UT-A3 is controlled at the transcriptional level by hypertonicity through binding of tonicity-responsive enhancer-binding protein (TonEBP) to the first promoter of the Slc14a2 gene (10, 11).

Synergy between ANG II and AVP control of urea transport is exemplified by the finding that ANG II increases AVP-mediated phosphorylation of UT-A1 and urea permeability of the rat inner medullary collecting duct (IMCD) (5).

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Fig. 1. Schematic illustration of PKC involvement in the regulation of aquaporin-2 (AQP2) and urea transporter UT-A1 by arginine vasopressin (AVP) and ANG II in the inner medullary collecting duct. TonEBP, tonicity-responsive enhancer-binding protein; V2, vasopressin type 2 receptor; AT1, ANG II type 1 receptor.
The role of PKC-α in urine concentration has been the focus of a recent study (6) on the short-term regulation of urea transport by hyperosmolality, stemming from previous findings (2) that hyperosmolality stimulates urea transport in perfused tubules. Klein et al. (6) showed that activation of UT-A1 by hyperosmolality is mediated by PKC-α phosphorylation of UT-A1 at one as-yet-undetermined consensus site, different from the Ser486 phosphorylated by PKA. These observations were conducted on isolated terminal IMCDs of rats and mice, including PKC-α-deficient mice, which excrete mildly diluted urine and have reduced abundance of UT-A1 compared with wild-type control mice. In IMCD suspensions from PKC-α-deficient mice, hypertonicity fails to induce UT-A1 phosphorylation, supporting the role of PKC-α in the upregulation of UT-A1 activity.

In the study by Thai et al. (12), the authors more specifically investigated the role of PKC as a mediator of ANG II-induced regulation of urea and water transport in the inner medulla. The effect of ANG II was tested in PKC-α-deficient mice, and ANG II increased the excretion of diluted urine in treated PKC-α−/− mice but not in control mice. This finding suggests that PKC is protective toward reduced AQP2 and impairment of urine concentration due to ANG II.

The reduced ability of ANG II-treated PKC-α−/− mice to concentrate urine was associated with a decreased abundance of medullary AQP2.

The decreased abundance of AQP2 appeared to be caused by decreased gene transcription, resulting from decreased phosphorylation of the transcription factor CREB. While CREB phosphorylation is known to be PKA mediated, these findings suggest that PKC may play a role as well and that PKC-α may affect directly or indirectly CREB phosphorylation downstream of ANG II. Although PKC-α activation of CREB has been previously described in cultured cells (8), it was not tested in vivo before. This study shows that a regulatory coordination exists between PKC-α and PKA.

Both AQP2 and UT-A1 are regulated by ANG II. However, although AQP2 was decreased in ANG II-treated PKC-α−/− mice, the abundance of UT-A1 was unchanged, and the abundance and phosphorylation of TonEBP, which controls transcription of UT-A1, was also unchanged.

This lack of effect of ANG II on TonEBP and UT-A1 suggests that different pathways mediate ANG II regulation of AQP2 and UT-A1.

Since both AQP2 and UT-A1 are regulated by AVP and ANG II, the difference in signaling pathways could be the mechanism that permits specificity in the regulation of water and urea transport.

An interesting observation from this study is that ANG II infusion per se did not result in increased AQP2 expression in wild-type mice, which leads to legitimate speculations about the role of other kinases and phosphatases that may be activated in parallel and stabilize the transcriptionally active form of CREB. A recent study (4) has implicated calcineurin in the dephosphorylation of UT-A1 and decreasing its abundance at the apical membrane, indicating that phosphatases may directly affect the activity of water and urea transporters and may potentially influence their degradation and half-life. (Fig. 1).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: S.M.B. conception and design of research; S.M.B. performed experiments; S.M.B. analyzed data; S.M.B. interpreted results of experiments; S.M.B. prepared figures; S.M.B. drafted manuscript; S.M.B. edited and revised manuscript; S.M.B. approved final version of manuscript.

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