Critical role of PPARγ in water balance

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 Peroxisome proliferator-activated receptor (PPAR-γ) is one of the three PPAR subtypes (PPARα, PPARβ/δ, and PPARγ) that are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily (7, 12, 13, 19). Far beyond the stimulation of peroxisome proliferation in rodents after which they were initially named, PPARs control the transcription of large number of genes involved in diverse physiological processes, such as metabolism of glucose and lipids, adipogenesis, insulin sensitivity, immune response, cell growth and differentiation, as well as pathophysiological conditions, such as metabolic syndrome, oxidative stress, inflammation, atherosclerosis and cancer, etc. In line with their diverse functions, PPARs present in a large variety of cell types and tissues, including in the kidneys, and have been shown to participate in the regulation of fluid homeostasis (2, 3, 7, 14, 19). Among the three PPARs, the role of PPARγ in fluid homeostasis has been most extensively investigated. Mostly utilizing the agonist of PPARγ, studies have demonstrated that activation of PPARγ promotes fluid retention by stimulating sodium reabsorption in the kidneys through different mechanisms involving epithelial sodium channels (ENaC), Na+/K+-ATPase, Na+/H+ exchangers, and Na+/HCO3- cotransporter, etc. (2, 7, 14). It is thus well recognized that PPARγ modulates renal sodium reabsorption. However, little is known regarding the role of PPARγ in the regulation of water balance, in particular, under physiological conditions. A seminal article in this issue of Physiological Genomics by Zhou et al. (23) has revealed a critical role of PPARγ in renal water reabsorption using PPARγ knockout (KO) mice.

The present study by Zhou et al. (23) demonstrates that mice with inducible global KO of PPARγ developed severe polyuria and reduced urine osmolality, accompanied by polydipsia and hyperphagia; furthermore, restriction of food and water intake did not alter the increase in urine volume and the decrease in urine osmolality and resulted in a dramatic loss of body weight and a significant increase in hematocrit in KO mice, which ruled out the influence of polydipsia and hyperphagia on the changes of urinary excretion in KO mice. There was no change in urinary excretion of sodium, potassium, and chloride, further indicating a defect in water reabsorption in KO mice. These findings suggest an essential role of PPARγ in urine concentrating capability. Mechanistically, this study found that there was no difference in urinary AVP excretion between KO and control mice under basal conditions or after water depletion, suggesting that deletion of PPARγ induced a nephrogenic diabetes insipidus but not central diabetes insipidus. More interestingly, this study showed that the vasopressin (AVP)/cAMP/aquaporin (AQP)-2 axis was intact in KO mice, as the total abundance or phosphorylation of AQP2 in the kidney or AVP-induced cAMP production in the inner medullary collecting duct suspensions was not suppressed in KO mice. Despite the functional AVP/cAMP/AQP2 axis in KO mice, both acute and chronic 1-desamino-8-D-arginine vasopressin treatment did correct the defect of urine concentrating capability in KO mice, which indicates that PPARγ regulates urine concentrating via AVP/AQP2-independent pathways. Taken together, this study not only unravels a novel function of PPARγ in regulating water transport but also uncovers a novel mechanism in urine concentrating associated with PPARγ signaling.

The findings in the study raise a number of interesting questions. First, whether these results have potential implications in physiological and pathological processes other than renal fluid reabsorption. The authors have suggested that their results support PPARγ as a key mediator that integrates the status of energy metabolism with renal excretory function and that a better understanding of this pathway may provide insights into the mechanism of disturbance of fluid metabolism associated with metabolic syndrome, as obesity is associated with increased renal fluid reabsorption. To extend the potential impact of the provocative findings from this study, a critical role of PPARγ in water transport may be implicated in cellular functions outside of the kidneys, because AQPs and water transport also play important roles in various physiological and pathological processes in other organ systems, for example, cell proliferation, vascular permeability, neuroexcitation, airway mucus production, inflammation, peripheral and organ edema, ischemic/reperfusion injury, tumorigenesis, etc. (20, 21). It is well known that PPARγ participates in a large variety of cellular processes (12, 13, 19), most of which overlap with those involving AQPs and water transport. The interaction between AQPs and PPARγ may exist in the mechanisms regulating cell functions or in the development of different diseases. Therefore, regulation of water transport by PPARγ may represent a novel mechanism contributing to PPARγ-mediated effects in different cell types and tissues, not only in the kidneys.

Second, whether PPARγ-mediated water reabsorption contributes to PPARγ agonist-induced fluid retention, and if so, whether targeting water reabsorption can be used as a therapeutical strategy for PPARγ-induced fluid retention. PPARγ agonists Thiazolidinediones (TZDs) are highly effective in Type 2 diabetes. However, fluid retention is the most important side effect that restricts the clinical use of this class of drugs (2, 6). Although it has been suggested that TZDs induce fluid retention by increasing sodium transport via ENaC in the collecting duct, many studies show contradictory results that do not support such a conclusion (2, 6, 7, 14). The mechanisms mediating TZD-induced fluid retention are apparently multifactorial and remain to be clarified (2, 6, 7, 14). The findings in the study by Zhou et al. (23) provide strong evidence for the possible involvement of water transport in TZD-induced fluid...
retention. In addition, it has been shown that TZD-induced fluid retention is often resistant to diuretics and is relieved only by drug withdrawal (2). If enhanced water reabsorption contributes to the TZD-induced fluid retention, targeting water reabsorption could be a potential alternation for eliminating TZD-induced fluid retention. The finding by Zhou and coworkers that PPARγ regulates water balance provides support for such a notion. There are actually clues that water retention may take part in the mechanisms of TZD-induced fluid retention. Previous work by the same authors has shown that PPARγ agonist accelerates plasma volume expansion in db/db mice and that inappropriate response of renal water transporters plays a significant role (24). TZD has also been shown to significantly reduce urinary volume and free water clearance without changing urinary sodium excretion in rats (4). It is thus worth investigating such a possibility that targeting water reabsorption for the management of TZD-induced fluid retention.

The Zhou et al. study did not show changes in renal AQP2 in PPARγ KO mice, which brings out a discrepancy in the effect of PPARγ on AQP2. PPARγ agonists have been shown to reduce the levels of AQP2 in normal animals (18, 24), whereas they have no effect on AQP2 in animals with nephrotic syndrome and obesity (24, 25) and restore the decreased levels of AQP2 in nephrotoxic animals (10, 11). Investigating the mechanisms mediating different effects of PPARγ on AQP2 may help to clarify the role of PPARγ in water balance under different conditions.

In addition, what is the mechanism by which PPARγ regulates water reabsorption in the kidneys? The basal and water depletion-induced AVP levels are unaffected in KO mice, which is consistent with the fact that PPARγ agonists modulate renal sodium handling not through the regulatory neurohormonal pathways (2). The unaffected AVP/cAMP/AQP2 axis suggests that the defect of urine concentrating in KO mice is not due to the impairment in the site where AQP2 is located, which is supported by previous reports showing that collecting duct-specific deletion of PPARγ did not affect fluid metabolism under physiological condition (5, 22). The authors proposed a possibility that PPARγ may target the thick ascending limb (TAL) to modulate AVP action, as AVP stimulates sodium reabsorption in the TAL, which contributes to urine concentrating capability. In addition, other types of AQPs that do not respond to AVP may need to be considered as potential targets of PPARγ and be responsible for the polyuria in KO mice. For example, PPARγ agonists have been shown to increase the levels of AQP1 in cultured human proximal tubule cells (15, 16) and AQP3 in rat kidney (9, 17). AQP1-null mice and AQP3-null mice both show severe polyuria (1, 8). It may be possible that deletion of PPARγ affects the levels of AQP1 and/or AQP3, which causes the defect of urine concentrating ability in PPARγ KO mice.

Collectively, although preliminary and lacks detailed mechanisms, the finding by Zhou and coworkers (23) that PPARγ plays a critical role in water metabolism is very intriguing and may stimulate further investigation on the cross-link between PPARγ signaling and water transport in various cellular processes in the kidneys as well as other tissue/organ systems, which may provide new insight into the functions of PPARγ and also suggest a new strategy to manipulate water transport via PPARγ pathway.

**REFERENCES**


