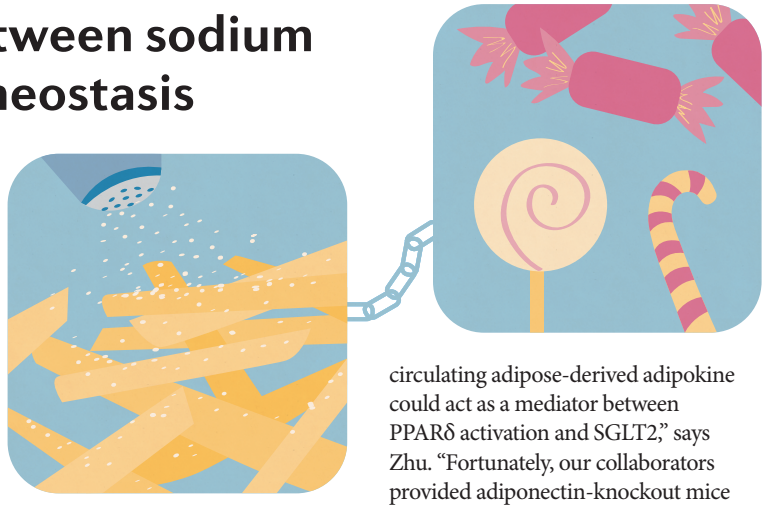
Nature Reviews Nephrology | Published online 12 Apr 2016; doi:10.1038/nrneph.2016.49

HYPERTENSION

PPARδ: a link between sodium and glucose homeostasis



Lara Crow/NPG

High sodium intake is a risk factor for hypertension, which increases the risk of adverse cardiovascular outcomes and mortality in patients with diabetes, but whether sodium and glucose homeostasis share common regulatory mechanisms is not clear. New findings show that the peroxisome proliferator-activated receptor PPARδ regulates natriuresis and glucose homeostasis by inducing the inhibition of the renal sodium–glucose cotransporter 2 (SGLT2) by adiponectin. "We reveal that high sodium intake promotes urinary sodium excretion and glycosuria by increasing plasma adiponectin levels through the upregulation of PPARδ in adipose tissue," explains researcher Zhiming Zhu. "Adiponectin downregulates renal SGLT2, which in turn reduces the reabsorption of sodium and glucose; however, this mechanism is dampened by hyperglycaemia in diabetes."

To examine potential interactions between sodium and glucose, Zhu and colleagues investigated the role of PPARδ in sodium transport and glucose reabsorption in the kidney. "Previous studies showed that adiponectin is secreted by adipose tissue and that its production is stimulated by PPARδ activation," says Zhu. "We previously demonstrated that activation of adipose PPARδ by telmisartan can prevent high-fat-diet-induced obesity and improves insulin resistance, and others have shown that angiotensin-II-receptor blockers can increase plasma adiponectin level and inhibit renal SGLT2 expression in diabetic rats. We therefore hypothesized that PPARδ participates in sodium transport and glucose reabsorption, resulting in improved sodium and glucose homeostasis under diabetic conditions."

> "High sodium promotes natriuresis and glycosuria by activating adipose PPARδ"

Using mice fed a high sodium diet (HSD) the researchers found that sodium intake increased sodium excretion and upregulated the expression of PPARδ in perirenal fat. Adipose-specific deletion of PPARδ attenuated the effect of a HSD on sodium excretion and exacerbated sodium-induced elevations in blood pressure. Adipose-specific PPARδ-knockout mice also had higher fasting blood glucose levels in response to a HSD than did control mice, indicating a role for PPARδ in the regulation of glucose homeostasis and natriuresis in response to high sodium levels.

To investigate the mechanisms by which PPARδ promotes natriuresis and glycosuria, Zhu and co-workers examined the expression of SGLT2 in control and adipose-specific PPARδ-knockout mice. Although high sodium intake reduced expression of SGLT2 in the renal cortex of control mice, expression of SGLT2 was unchanged by sodium in the knockout mice. Administration of the SGLT2 inhibitor dapagliflozin, however, increased natriuresis and glycosuria in both control and knockout mice on a HSD, suggesting that PPARδ mediates its effects on natriuresis and glycosuria by inhibiting SGLT2. "We hypothesized that a circulating adipose-derived adipokine could act as a mediator between PPARδ activation and SGLT2," says Zhu. "Fortunately, our collaborators provided adiponectin-knockout mice enabling us to identify adiponectin as the crucial mediator that downregulates SGLT2 activity in response to PPARδ activation."

To assess the effects of hyperglycaemia on this process, Zhu and colleagues administered a HSD to control and diabetic *db*/*db* mice. The diabetic mice had an attenuated glucose-lowering and natriuretic response to the HSD compared with the control mice. The diabetic mice also had higher renal expression of SGLT2 than did controls and a blunted natriuresis and glycosuric response to dapagliflozin. "Our findings show that high sodium promotes natriuresis and glycosuria by activating adipose PPARδ, which reduces renal SGLT2 by increasing adiponectin levels," explains Zhu. "Furthermore, hyperglycaemia reduces urinary sodium excretion by augmenting SGLT2 activity, which impedes this pathway in diabetes and suggests that well-controlled hyperglycaemia might alleviate sodium retention in hypertensive diabetic patients."

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ORIGINAL ARTICLE Zhao, Y. *et al.* Sodium intake regulates glucose homeostasis through the PPARδ/adiponectin-mediated SGLT2 pathway. *Cell Metab.* http://dx.doi.org/10.1016/j.cmet.2016.02.019