JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
COMMENTARY

Salt and sugar: Bad company

BENEFICIAL EFFECT OF ADIPONECTIN ON THE KIDNEY DISEASES

Adiponectin is predominantly secreted from adipose tissues, physiological serum concentration reaches 5–30 μg/mL and it influences systemic homeostasis, such as sensitization of insulin actions and cardiovascular protections. In patients with obesity and type 2 diabetes, the serum adiponectin levels negatively correlate with body mass index and body fat mass, and they are lower compared with normal control subjects. Adiponectin levels in type 2 diabetes patients also negatively correlate with early features of nephropathy. In patients with established chronic kidney disease (stages 3 and 4), adiponectin levels are elevated, and the elevation of adiponectin levels predicts progression of disease and mortality. Adiponectin binds to two forms of receptors, AdipoR1 and AdipoR2. AdipoR1 is abundantly expressed in skeletal muscle, whereas AdipoR2 is predominantly expressed in liver tissue. In the kidney tissues, AdipoR1 is localized in podocytes and proximal tubular cells, and AdipoR2 has also been identified in proximal tubular cells. Adiponectin increases the activation of adenosine monophosphate-activated protein kinase, as well as the mitogen-activated kinase pathway. The adiponectin treatment proximal tubular cells (HK-2 cells) expressing AdipoR1 and AdipoR2 caused activation of adenosine monophosphate-activated protein kinase and decreased levels of the secretion of monocyte chemotactic protein-1. In podocytes, adiponectin treatment improves the glomerular podocyte foot processes fusion by the activation of adenosine monophosphate-activated protein kinase and downregulation of reduced nicotinamide adenine dinucleotide phosphate oxidase 4 production[1].

PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS AND KIDNEY

Peroxisome proliferator activated receptors (PPARs) are ligand-activated transcription factors of the nuclear receptor superfamily serving as a lipid sensor, and they are involved in the control of nutrition and energy metabolism. Three members of PPARs – PPARα, PPARδ, and PPARγ – are identified and recognized as key players of type 2 diabetes, and they are also important therapeutic targets. PPARα is mainly involved in fatty acid oxidation in the liver, heart and kidney, whereas PPARγ is a master regulator for adipogenesis and lipid synthesis in adipose tissues. PPARδ participates in fatty acid oxidation mainly in skeletal muscle and the heart. PPARs are also involved in the control of salt handling and blood pressure. PPARα and PPARδ ligands have been reported to lower blood pressure in experimental models of hypertension. However, PPARγ causing hypertension or hypotension remains controversial. The genetic ablation of PPARγ in mice shows the hypotensive phenotype, and it fits in the finding where PPARγ agonists, thiazolidinediones, stimulate the gene expression of renin in the kidney. PPARγ also enhances the expression of serine glucocorticoid kinase-1 and sodium hydrogen exchanger-3. Serine glucocorticoid kinase-1 then upregulates the several sodium transporters, such as epithelial sodium channels, which all contribute to the retention of sodium, edema and development of hypertension[2]. In contrast, thiazolidinediones suppress the vasoconstrictor effects of endothelin-1, angiotensin II and 5-hydroxytryptamine 2B receptor agonists.

SALT INTAKE AND GLUCOSE HOMEOSTASIS

The tight relationship between salt intake and blood pressure has been documented in observational studies and clinical trials, and the World Health Organization recommend a reduction to 5 g/day of salt in adults. However, recommending a very low salt intake in humans should be carefully considered. A randomized clinical trial documented that an extremely low sodium diet (<50 mEq/day in urinary sodium) generates a pro-inflammatory phenotype characterized by an increase in procalcitonin and tumor necrosis factor-α, and an opposite effect on an anti-inflammatory cytokine, such as adiponectin[3]. A recently published study by Zhao *et al.*[4] reported the relationship between sodium intake and the regulation of glucose homeostasis through PPARδ/adiponectin-mediated sodium-glucose cotransporter 2 (SGLT2) pathway. PPARδ agonists or gene manipulation showed that PPARδ activation alleviates dyslipidemia, hyperglycemia and insulin resistance. Importantly, PPARδ agonists exert renal protective effects in streptozotocin-induced diabetic mice by increasing the expression of anti-inflammatory co-repressor B-cell lymphoma-6, which subsequently suppressed monocyte chemotactic protein-1 and osteopontin expression[5]. Zhao *et al.*[4] fed wild-type ($PPAR\delta^{flox/flox}$) and adipose-specific PPARδ knockout (Fabp4-$PPAR\delta^{flox/flox}$) mice with a high-salt diet. Increased natriuresis and glycosuria, as well as reduced expression of SGLT2, were observed in $PPAR\delta^{flox/flox}$ mice, and they were blunted in Fabp4-$PPAR\delta^{flox/flox}$ mice. The activation of PPARδ by GW501516 increased expression of adiponectin in cultured adipocytes from $PPAR\delta^{flox/flox}$ mice, but such increased adiponectin was not observed in Fabp4-$PPAR\delta^{flox/flox}$ mice. The binding of important transcriptional activators, such as hepatocyte nuclear factor-1α and Sp-1 in the promoter region of SGLT2, and

*Corresponding author. Jun Wada
Tel.: +81-86-235-7232
Fax: +81-86-222-5214
E-mail address: junwada@okayama-u.ac.jp
Received 3 June 2016; revised 9 July 2016; accepted 12 July 2016

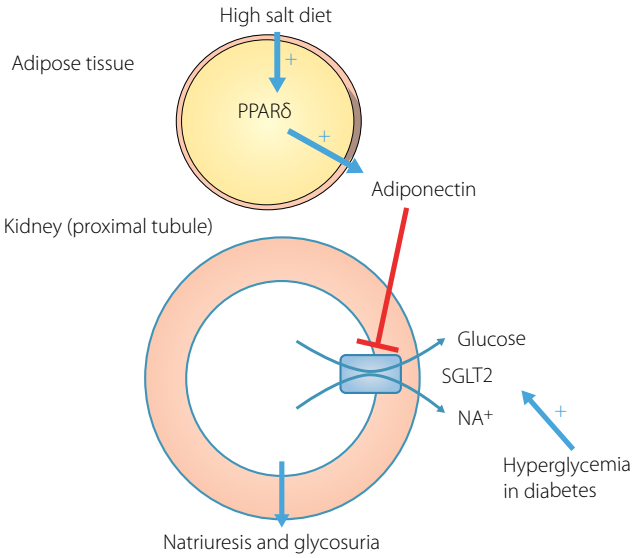

Figure 1 | Upregulation of sodium-glucose cotransporter-2 (SGLT2) under hyperglycemia and development of hypertension in diabetes. A high-salt diet activates peroxisome proliferator-activated receptor δ (PPARδ) and produces adiponectin from adipose tissues, which reduces SGLT2. Such processes are blunted as a result of increased SGLT2 activities in diabetes.

expression of the SGLT2 gene were significantly reduced by the treatment of adiponectin in human renal tubular epithelial cells, proximal tubular cell line. In diabetic *db*/*db* mice receiving a high-salt diet, high sodium intake-induced natriuresis is hampered as a result of increased SGLT2 activities. In patients with diabetes, higher glycated hemoglobin is associated with decreased levels of sodium excretion (Figure 1). The present study shed light on the unrecognized mechanism for hyperglycemia-induced sodium retention. The activation of PPARδ, elevation of serum adiponectin, and subsequent inhibition of SGLT2 might lead to natriuresis and glycosuria, and it might be beneficial in hypertensive diabetic patients.

DISCLOSURE

Jun Wada receives speaker honoraria from Astellas, Boehringer Ingelheim, Novartis and Tanabe Mitsubishi, and receives grant support from Astellas, Bayer, Chugai, Daiichi Sankyo, Kissei, Kyowa Hakko Kirin, MSD, Otsuka, Teijin, Torii, Pfizer, Takeda and Taisho Toyama.

Jun Wada*
Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

REFERENCES

1. Sharma K, Ramachandrarao S, Qiu G, *et al.* Adiponectin regulates albuminuria and podocyte function in mice. *J Clin Invest* 2008; 118: 1645–1656.
2. Guan Y, Hao C, Cha DR, *et al.* Thiazolidinediones expand body fluid volume through PPARgamma stimulation of ENaC-mediated renal salt absorption. *Nat Med* 2005; 11: 861–866.
3. Mallamaci F, Leonardis D, Pizzini P, *et al.* Procalcitonin and the inflammatory response to salt in essential hypertension: a randomized cross-over clinical trial. *J Hypertens* 2013; 31: 1424–1430; discussion 30.
4. Zhao Y, Gao P, Sun F, *et al.* Sodium Intake Regulates Glucose Homeostasis through the PPARdelta/Adiponectin-Mediated SGLT2 Pathway. *Cell Metab* 2016; 23: 699–711.
5. Matsushita Y, Ogawa D, Wada J, *et al.* Activation of peroxisome proliferator-activated receptor delta inhibits streptozotocin-induced diabetic nephropathy through anti-inflammatory mechanisms in mice. *Diabetes* 2011; 60: 960–968.

Doi: 10.1111/jdi.12553