Annexin 1 Mimetic Ac2-26 Holds Promise for the Treatment of Diabetic Nephropathy

Yu Pan,[1,2] Ming-Zhi Zhang,[1,2] and Raymond C. Harris[1,2,3]

Diabetes 2021;70:2183–2184 | https://doi.org/10.2337/dbi21-0030

In this issue of *Diabetes*, Wu et al. (1) report that in a high-fat diet/streptozotocin–induced diabetes model, global annexin 1 (ANAX1) deletion exacerbates diabetic nephropathy (DN), as indicated by increased albuminuria and macrophage infiltration, increased glomerular size, mesangial expansion, glomerular basement membrane thickness, and foot process effacement, increased tubulointerstitial injury, and fibrosis. They also detected lipid accumulation and mitochondrial abnormalities in the proximal tubule epithelial cells. RNA-sequencing analysis revealed a role of ANAX1 in lipid metabolism in the HFD/STZ-induced DN mice. Using a human immortalized proximal tubule epithelial cell line, HK-2 cells, they found that ANAX1 knockdown impaired mitochondrial fatty acid oxidation via a FPR2/AMPK/PPARα/CPT2b signaling pathway, leading to reduced intracellular lipid accumulation. ANAX1 knockdown also aggravated the lipid disorders in podocytes. Finally, administration of Ac2-26, an ANAX1 mimetic, ameliorated renal lipotoxicity in both diabetic ANAX1 knockout mice and diabetic *db/db* mice. In a recent study, the same group also reported that *ANAX1* overexpression ameliorated DN and that ANAX1 expression is upregulated and correlates with kidney function and outcomes from data from a cohort of patients with diabetes (1,2).

ANAX1, also known as lipocortin-1 or p35, was originally discovered as a Ca^{2+}-dependent substrate of the EGF receptor tyrosine kinase. It is a member of the annexin family of proteins that binds Ca^{2+} and phospholipids (3). Glucocorticoids exert their anti-inflammatory effect at least in part due to induction of ANAX1, which binds to membrane phospholipids through a calcium-dependent manner, resulting in inhibition of PLA2 and eicosanoid synthesis, including proinflammatory lipid mediators such as prostaglandins (4). Recent studies have indicated that the anti-inflammatory actions of ANAX1 are reproduced by Ac2-26 in many inflammatory and cellular settings (5,6). This peptide, as well as the whole protein, exerts its effects through activation of the formyl peptide receptor type 1 (FPR1) and type 2 (FPR2) (7). Ac2-26 has been shown to be beneficial in experimental models of organ injury, including inhibition of lung fibrosis (8) and brain injury (9).

In rat kidney, ANAX1 is expressed in the epithelia of Bowman's capsule, the macula densa, medullary/papillary collecting ducts, and thick ascending limb, and its expression in distal tubular epithelial cells, including macula densa, collecting ducts, and thick ascending limb, increases in response to acute ischemic injury (10). Surprisingly, ANAX1 expression is not detectable in proximal tubule. This may be explained by expression differences between rats and mice, or ANAX1 is upregulated in diabetes. ANAX1 is also expressed in immune cells, particularly in macrophages and neutrophils (5,6,11). Of note, in the brain, ANAX1 is expressed only in microglia, the immune cell of the central nervous system, where it is expressed at high levels (12). ANAX1 has been shown to have anti-inflammatory and proresolving actions via regulation of macrophage polarization and efferocytosis. ANAX1 and Ac2-26 have been reported to inhibit cell proliferation and induce phagocytosis of apoptotic neutrophils by macrophages (13). Therefore, ANAX1 mimetics hold great potential as a therapeutic target for many inflammatory conditions, including DN, as indicated in the current study. In future studies, selective deletion of ANAX1 in distal epithelial cells is needed to confirm its role in the segment. In addition, the selective deletion of ANAX1 in immune cells may provide further insights into its role in protection against the development of DN.

[1]Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
[2]Vanderbilt Center for Kidney Disease, Vanderbilt University Medical Center, Nashville, TN
[3]Department of Veterans Affairs Hospital, Nashville, TN
Corresponding author: Raymond C. Harris, ray.harris@vumc.org

See accompanying article, p. 2192.

Funding. These studies were supported by National Institute of Diabetes and Digestive and Kidney Diseases, National institutes of Health, grants DK51265, DK95785, DK62794, and P30DK114809 (to R.C.H. and M.-Z.Z.); VA Merit Award 00507969 (R.C.H.); the Vanderbilt Center for Kidney Disease; and National Natural Science Foundation of China grant 81870490 (Y.P.).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Wu L, Liu C, Chang D-Y, et al. The attenuation of diabetic nephropathy by annexin A1 via regulation of lipid metabolism through the AMPK/PPARα/CPT1b pathway. Diabetes 2021;70:2192–2203

2. Wu L, Liu C, Chang DY, et al. Annexin A1 alleviates kidney injury by promoting the resolution of inflammation in diabetic nephropathy. Kidney Int 2021;100:107–121

3. McKanna JA, Cohen S. The EGF receptor kinase substrate p35 in the floor plate of the embryonic rat CNS. Science 1989;243:1477–1479

4. Gerke V, Creutz CE, Moss SE. Annexins: linking Ca2+ signalling to membrane dynamics. Nat Rev Mol Cell Biol 2005;6:449–461

5. Perretti M, D'Acquisto F. Annexin A1 and glucocorticoids as effectors of the resolution of inflammation. Nat Rev Immunol 2009;9:62–70

6. Perretti M, Dalli J. Exploiting the Annexin A1 pathway for the development of novel anti-inflammatory therapeutics. Br J Pharmacol 2009;158:936–946

7. Ernst S, Lange C, Wilbers A, Goebeler V, Gerke V, Rescher U. An annexin 1 N-terminal peptide activates leukocytes by triggering different members of the formyl peptide receptor family. J Immunol 2004;172:7669–7676

8. Trentin PG, Ferreira TP, Arantes AC, et al. Annexin A1 mimetic peptide controls the inflammatory and fibrotic effects of silica particles in mice. Br J Pharmacol 2015;172:3058–3071

9. Gong J, Tai QH, Xu GX, et al. Ac2-26 alleviates brain injury after cardiac arrest and cardiopulmonary resuscitation in rats via the eNOS pathway. Mediators Inflamm 2020;2020:3649613

10. McKanna JA, Chuncharunee A, Munger KA, Breyer JA, Cohen S, Harris RC. Localization of p35 (annexin I, lipocortin I) in normal adult rat kidney and during recovery from ischemia. J Cell Physiol 1992;153:467–476

11. Wallner BP, Mattaliano RJ, Hession C, et al. Cloning and expression of human lipocortin, a phospholipase A2 inhibitor with potential anti-inflammatory activity. Nature 1986;320:77–81

12. McKanna JA, Zhang MZ. Immunohistochemical localization of lipocortin 1 in rat brain is sensitive to pH, freezing, and dehydration. J Histochem Cytochem 1997;45:527–538

13. Scannell M, Flanagan MB, deStefani A, et al. Annexin-1 and peptide derivatives are released by apoptotic cells and stimulate phagocytosis of apoptotic neutrophils by macrophages. J Immunol 2007;178:4595–4605