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Kidney ADP-Ribosyl Cyclase Inhibitors as a Therapeutic Tool for Diabetic Nephropathy

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1. Introduction

ADP-ribosyl cyclases (ADPR-cyclases)/CD38 have emerged as effecter molecules for generating novel Ca^{2+} signaling messengers, cyclic ADP-ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP) (1, 2) (see Figure 1). Mounting evidence has indicated that G protein-coupled receptors, including the angiotensin II (Ang II) receptor, mediate activation of ADPR-cyclase to generate Ca^{2+} signaling messengers (3-5). We have studied Ang II receptor-mediated activation of ADPR-cyclase, resulting in Ca^{2+} dysfunction

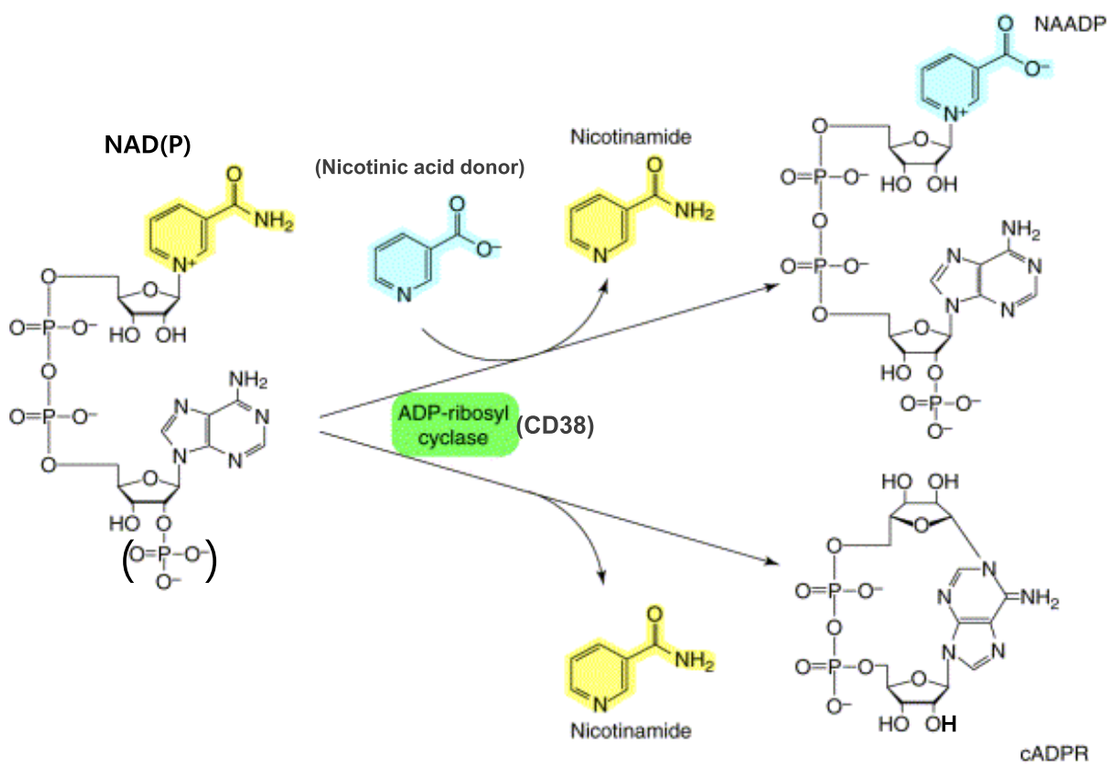

Fig. 1. CD38/ADPR-cyclase-catalyzed reactions for the production of two Ca^{2+} mobilizing second messengers, NAADP and cADPR.

which plays an important role in the pathogenesis of renal failure using an in vitro and an in vivo model (4, 6). In this review article, I would like to give an overview on the current worldwide status of diabetic nephropathy (DN) as a leading cause of end-stage renal disease (ESDR), the causative role of renin-angiotensin-aldosterone system (RAAS) for DN, the role of ADPR-cyclase in pathogenesis of DN and a potential therapeutic tool for DN by the intervention of Ang II receptor-mediated Ca^{2+} signaling with a kidney-specific ADPR-cyclase inhibitor.

2. Diabetic nephropathy and the renin-angiotensin-aldosterone system

Chronic kidney disease (CKD) is a major worldwide public-health problem affecting about 10% of the population (7). CKD has an increased annual incidence rate of about 5–8% (8). A leading cause of CKD is diabetic nephropathy (DN) throughout much of the world. This disease is characterized by the thickening of the glomerular basement membrane and mesangial matrix expansion (9). The early stage of DN is associated with glomerular hyperfiltration and glomerular hypertrophy, but not the collapse of the glomerular capillaries. DN results from an interaction between metabolic and hemodynamic factors. Glucose-dependent pathways are activated within the diabetic kidney, such as increasing oxidative stress, polyol formation, and advanced glycation end product accumulation (10).

In addition to elevated blood glucose, hypertension and inappropriate activation of the RAAS have been identified as contributing to the development and progression of diabetic renal disease (11). Clinical studies have demonstrated an important role for blood glucose control in reducing the development and progression of DN (12, 13) and they also have shown the importance of blood pressure reduction (14, 15) and the blockade of the RAAS (16–18) in slowing the progression of renal dysfunction in diabetes.

The pharmacological inhibition of the RAAS with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs) are the first-line treatments for CKD patients. Despite several advantages of these agents, a number of side-effects do occur (19-21). Moreover, the incidence of end-stage renal disease as a result of diabetes continues to rise in the world.

RAAS is a major regulatory system of cardiovascular and renal function. The final step of the RAAS cascade is the activation of Ang II receptors by Ang II. In the kidney, Ang II plays critical roles in the regulation of the glomerular filtration rate (GFR) and renal blood flow, and salt water retention (22-24). Effects of Ang II are mediated by at least two structurally and pharmacologically distinct Ang II type 1 and 2 receptors (AT1R and AT2R, respectively) (23, 24). The physiological and pathophysiological effects of Ang II are mainly exerted by AT1R activation (24-26) via complex interacting signaling pathways involving the primary stimulation of phospholipase C (PLC) and Ca^{2+} mobilization and the secondary activation of protein tyrosine kinase (PTK), extracellular signal-regulated kinases-1 and -2, and phosphatidylinositol 3-kinase (PI3K)-dependent kinase Akt (23-26). We extended these signaling pathways mainly focusing on the molecular basis of Ca^{2+} signaling by ADPR-cyclase activation in Ang II signaling in murine mesangial cells (MMCs) and other cells (see below).

3. ADP-ribosyl cyclase (ADPR-cyclase)/CD38

CD38, a type II transmembrane glycoprotein, represents a mammalian ADPR-cyclase and is involved in T cell activation (27) and oxytocin secretion, which is closely associated with

social behavior (28). CD38 acts mainly as an NAD glycohydrolase therewith regulating intracellular NAD levels (29, 30). CD38 was initially identified as a cell surface marker on thymocytes and T lymphocytes, showing discrete expression during lymphocyte differentiation (31). Further studies revealed that CD38 expression is ubiquitous in the immune system as well as in various organs, including prostate epithelial cells, pancreatic islet cells, and brain cells (32-35). From a study on new intracellular messengers in the sea mollusk *Aplysia*, a surprising finding of the striking similarity between human CD38 and the ADPR-cyclase enzyme purified from *Aplysia* was made (36). ADPR-cyclase generates two important Ca^{2+}-mobilizing second messengers, cADPR and NAADP, from NAD^+ and $NADP^+$, respectively (37-39). The second messenger, cADPR, increases intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) through the release of Ca^{2+} from intracellular endoplasmic reticulum (ER) stores via ryanodine receptors and/or Ca^{2+} influx through plasma membrane Ca^{2+} channels (5, 39,40, 41). The other second messenger, NAADP, increases intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) through the release of Ca^{2+} from a discrete intracellular store, called acidic organelles, via Two-pore channels (TPCs) (42). Production of NAADP by ADPR-cyclases including CD38 is stimulated by various G protein-coupled receptors (GPCRs), including, AT1R (43, 44).

Mounting evidence has indicated that ADPR-cyclase(s) other than CD38 may exist in the kidney, brain, and the heart (40, 45), including various cells (30, 45-47). The first clues to the existence of novel ADPR-cyclase(s) emerged from experiments of the comparison of tissue cADPR levels in CD38 wild type and knockout mice (40). Levels of cADPR in spleen, bone marrow and lungs of CD38 knockout mice were significantly decreased, compared to those of CD38 wild type mice, whereas levels of cADPR in brain, heart and kidneys of CD38 knockout mice were comparable to those of CD38 wild type mice (40). These results suggest that ADPR-cyclase(s) other than CD38 may exist in the kidney, brain, and the heart. We recently demonstrated that Ang II-stimulated Ca^{2+} signals were not significantly different between CD38 wild type and CD38 knockout cardiomyocytes (48). However a cADPR antagonistic analog, 8-bromo-cADPR (8-Br-cADPR) completely inhibited the Ang II-induced sustained Ca^{2+} increase. These findings indicate that cADPR is generated by a novel unidentified ADPR-cyclase other than CD38. In addition, a bisphenyl compound 4,4'-dihydroxyazobenzene (4-DAB) has been shown to inhibit kidney ADPR-cyclase, but not CD38, with a high potency (47). The kidney ADPR-cyclase inhibitor inhibits kidney ADPR-cyclase activity with a 10,000-fold more potency than it does with heart ADPR-cyclase activity. However, an analog of 4-DAB, 2,2'-dihydroxyazobenzene (2-DAB), inhibits kidney and heart ADPR-cyclase activity with similar effects (see below). These results suggest that ADPR-cyclases in the kidney and the heart are different. Therefore, the signaling pathways of Ang II-induced ADPR-cyclase activation in rat cardiomyocytes (48) and mesangial cells (4) are different due to different ADPR-cyclases (see below).

4. The role of ADPR-cyclase/CD38 in GPCR-mediated Ca^{2+} signaling

Evidence from our and other laboratories has indicated that various G protein-coupled receptors (GPCRs) mediate the activation of ADP-ribosyl cyclase (ADPR-cyclase) (3-6). ADPR-cyclase-involved GPCRs include the β-adrenergic receptor, muscarinic receptor, interleukin 8 receptor (IL8R) and AT1R. The mechanism by which GPCR activates ADPR-cyclase was discovered from the functional loop involving IL-8 and CD38 in lymphokine-activated killer (LAK) cells (5). Stimulation of IL8R results in protein kinase G-dependent phosphorylation of nonmuscle myosin heavy chain IIA (MHCIIA) and the association of

phosphorylated MHCIIA with CD38 through Lck, which are essential for CD38 internalization for cADPR formation (49). Ensuing cADPR-mediated Ca^{2+} release from ER stores induces NAADP production by Rap1 activation via cAMP/Epac/PKA, resulting in the release of Ca^{2+} from lysosome-related acidic organelles (44). Although the result of IL8-mediated CD38 activation mechanism in LAK cells shows us one representative model, whether a similar mechanism by which other GPCRs use to activate ADPR-cyclase in other cells as that in IL8R-LAK cells remains to be clarified.

Initially we assumed that ADPR-cyclase plays a role in Ang II receptor-mediated Ca^{2+} signaling in the kidney. Therefore, we chose mouse mesangial cells (MMCs) as a model system to study Ang II signaling because MMCs are believed to be the center for the pathogenesis of CKD (4). Treatment of MMCs with Ang II induced an increase in intracellular Ca^{2+} concentrations through a transient Ca^{2+} release via an inositol 1,4,5-trisphosphate receptor (IP_3R) and a sustained Ca^{2+} influx via L-type Ca^{2+} channels. The sustained Ca^{2+} signal, but not the transient Ca^{2+} signal, was blocked by 8-Br-cADPR, and an ADPR cyclase inhibitor, 4-DAB. In support of the results, 4-DAB inhibited Ang II-induced cADPR production. Application of pharmacological inhibitors revealed that the activation of ADPR-cyclase by Ang II involved AT1R, PI3K, PTK, and PLC-γ1 (Figure 2).

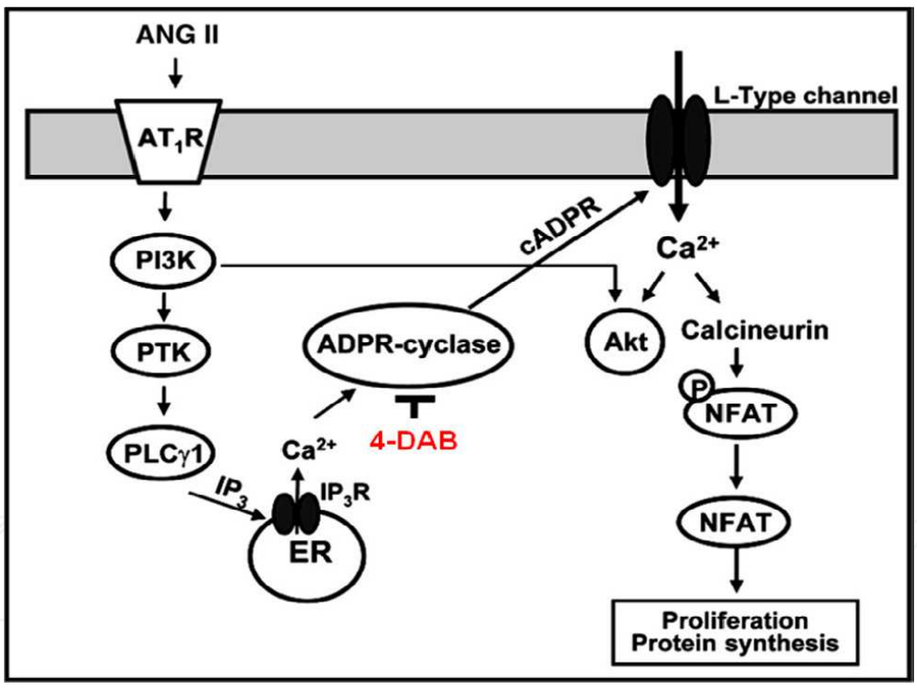

Fig. 2. Schematic model of ADPR-cyclase activation in Ang II signaling pathway (adopted from [4]). Stimulation of AT1R by Ang II leads to sequential activation of PI3K, PTK, and PLCγ1, in turn causing a Ca^{2+} release by IP_3R from ER, resulting in activation of ADPR-cyclase. Activation of ADPR-cyclase induces Ca^{2+} influx via L-type calcium channels, Akt phosphorylation, NFAT nuclear translocation, cell proliferation, and protein synthesis. 4-DAB abrogates the sustained Ca^{2+} signal, thereby blocking downstream events.

Moreover, 4-DAB as well as 8-Br-cADPR abrogated Ang II-mediated Akt phosphorylation, nuclear translocation of nuclear factor of activated T cell (NFAT), and the uptake of

[^{3}H]thymidine and [^{3}H]leucine in MMCs. These results demonstrate that ADPR-cyclase in MMCs plays a pivotal role in Ang II signaling for cell proliferation and protein synthesis. The Ang II-induced ADPR-cyclase activation has also been observed in rat cardiomyocytes (48) and MMCs (4), and hepatic stellate cells (50), although the signaling pathways in those cells are different from each other (see below, Figure 3).

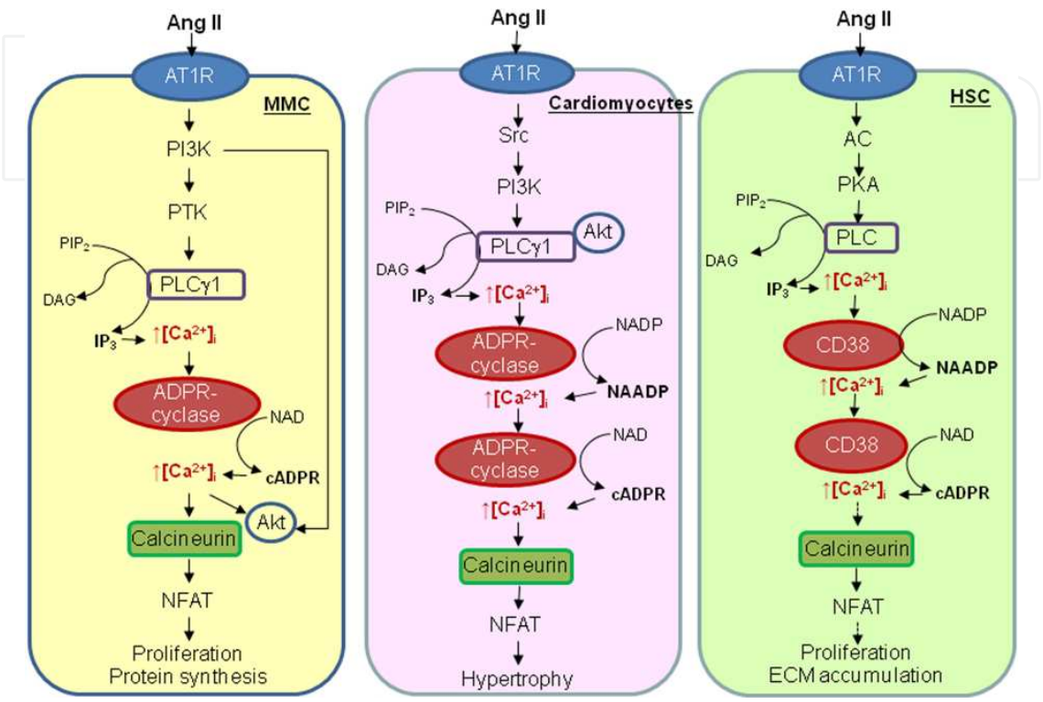

Fig. 3. Variation on the theme of angiotensin II-induced Ca^{2+} signaling. AT1R, angiotensin II type 1 receptor; MMC, mouse mesangial cell; HSC, hepatic stellate cell.

5. The discovery of a small-molecule inhibitor for kidney ADPR-cyclase and its application to diabetic nephropathy

In order to get small-molecule inhibitors of kidney ADPR-cyclase, which make it possible to elucidate the involvement of ADPR-cyclase/cADPR in Ang II signaling in the kidney (4, 6), we screened a chemical library of approximately 10,000 compounds using a partially purified ADPR-cyclase from rat kidneys (47). This screen resulted in the selection of 4-DAB as a small molecule inhibitor (Figure 4). The compound was able to inhibit the generation of cGDPR and ε-ADPR from NGD^+ and ε-NAD^+, respectively, by the kidney ADPR-cyclase in a concentration-dependent manner. These data suggest that the compound may bind to the active site of the enzyme. Half maximal inhibition (IC_{50}) of the enzyme activity was approximately 100 μM. CD38 and ADPR-cyclases partially purified from rat brain, heart, and spleen tissues were insensitive to 4-DAB at 200 μM.

Although a number of GPCRs have been shown to utilize ADPR-cyclase in the regulation of $[Ca^{2+}]i$, we chose the extracellular calcium ion ($[Ca^{2+}]_o$)-sensing receptor (CaSR) to test 4-DAB as a possible candidate inhibitor of ADPR-cyclase in MMCs. Stimulation of CaSR with $[Ca^{2+}]_o$ resulted in a significant increase of [cADPR]i and a generation of long-lasting increase of $[Ca^{2+}]i$, involving an initial peak rise followed by a sustained increase that was gradually

decreased. The sustained Ca^{2+} signal, but not the initial peak, was blocked by pre-treatment with 8-Br-cADPR. On the basis of these results that show the stimulation of CaSR activates ADPR-cyclase in MMC, we next evaluated 4-DAB as a possible candidate inhibitor of ADPR-cyclase. This compound was able to inhibit $[Ca^{2+}]_o$-mediated later sustained elevation of $[Ca^{2+}]i$ but not the initial rise of $[Ca^{2+}]i$ in a dose-dependent manner. Further, $[Ca^{2+}]_o$ -induced production of cADPR was also blocked by pre-treatment of 4-DAB in a concentration-dependent manner. IC_{50} was approximately 2.5 nM. In addition, since it has been reported that CaSR-mediated Ca^{2+} signals is involved in MMC proliferation, we examined whether 4-DAB inhibits the $[Ca^{2+}]_o$-induced MMC proliferation and demonstrated that the $[Ca^{2+}]_o$-induced increment of proliferation was also inhibited by 4-DAB in a similar range of concentrations observed in the inhibition of the sustained Ca^{2+} signal.

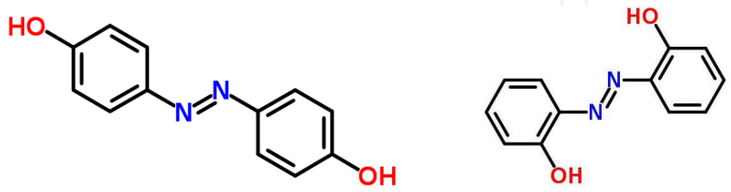

Fig. 4. Structure of 4,4′-dihydroazobenzene (4-DAB), left, and 2,2′-dihydroazobenzene (2-DAB), right.

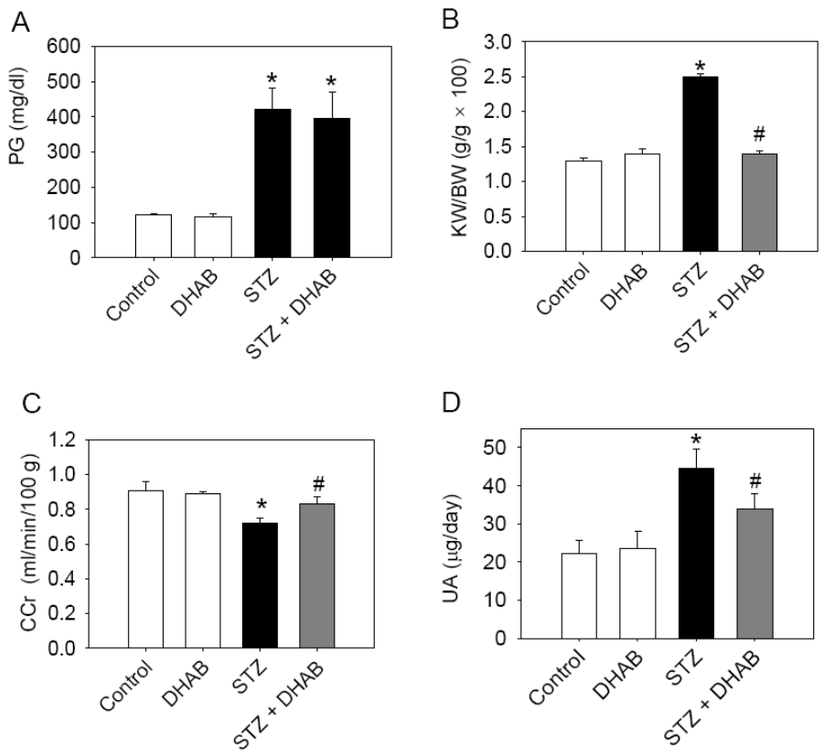

Fig. 5. Effect of 4,4′-dihydroazobenzene (DHAB) on streptozotocin (STZ)-treated mice. (adopted from [6]). A: Plasma glucose level (PG), B: Ratio of kidney weight per body weight (KW/BW), C: Creatinine clearance (CCr) level, and D: Urinary albuminuria (UA) of 6 wk diabetic and control mice after DHAB treatment. Data are means ± SE. *P < 0.05 vs. control, #P < 0.05 vs. STZ group.

We utilized the specific inhibitor for kidney ADPR-cyclase to corroborate the evidence that there are ADPR-cyclases different from CD38. We utilized a human T cell-derived cell line, Jurkat T cell, which exclusively expresses CD38 that is regulated by CD3/TCR (51). Treatment of Jurkat T cells with OKT3, which is a ligand for CD3/TCR, showed a typical biphasic increase of $[Ca^{2+}]i$, involving an initial peak rise followed by a sustained increase. Pre-treatment with 8-Br-cADPR inhibited only the sustained Ca^{2+} rise. In contrast, 4-DAB did not show any effects on OKT3-mediated Ca^{2+} rise even at 10 μM.

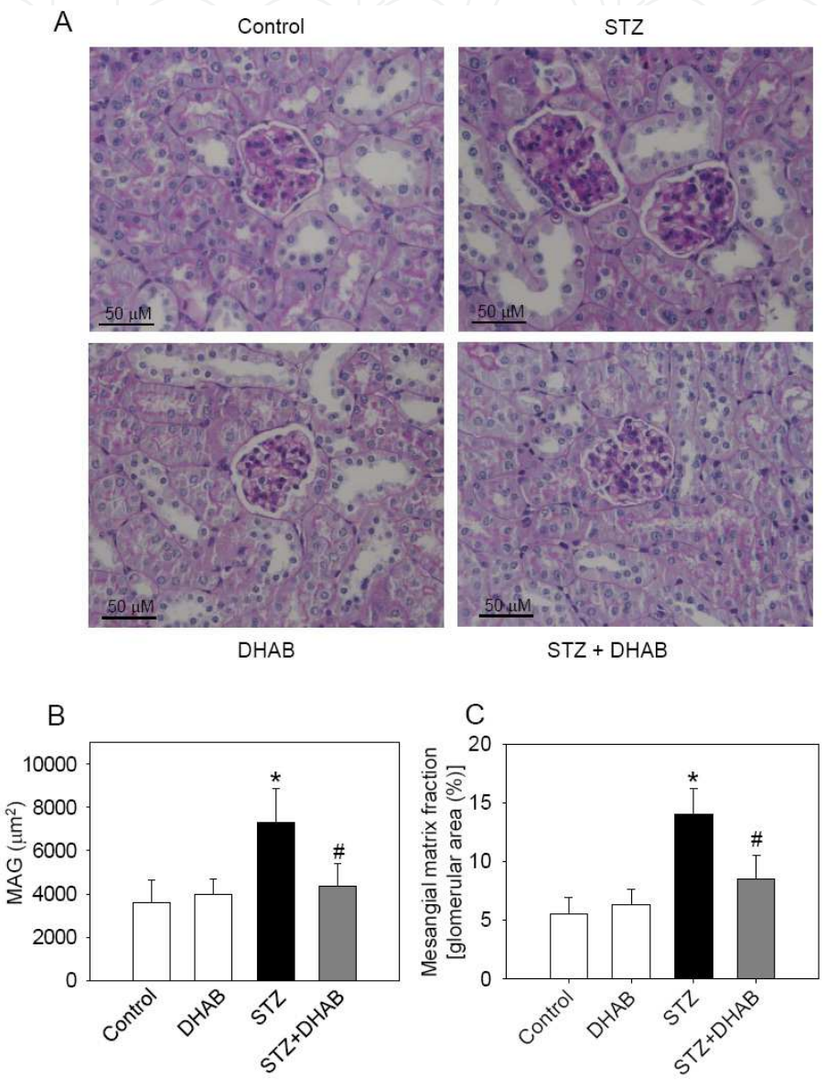

Fig. 6. Light microscopic appearance of glomeruli. (adopted from [6]). A: Representative photomicrographs of the kidney sections stained with periodic acid-Schiff (PAS). Scale bars; 50 μm. B: Quantification of glomerular size from A. Glomerular cross-sectional areas were determined by using a computer-assisted color image analyzer. MAG; mean area of glomeruli. C: Quantification of extracellular mesangial matrix expansion is expressed as PAS-positive mesangial material per total glomerular tuft cross-sectional area (mesangial area/total glomerular tuft area X 100). Values are means ± SE from 25 individual glomeruli in kidney sections from 6 mice in each group. *P < 0.05 vs. control; #P < 0.05 vs. STZ.

Based on our earlier observation that 4-DAB was a potent inhibitor of kidney ADPR-cyclase and could protect Ang II-mediated mesangial cell growth (4, 47), we further investigated the effects of 4-DAB on a mouse model of DN (6). Male mice were randomly assigned to normal control and diabetic groups of comparable age. The diabetic group received 45 μg/kg of 4-DAB for 6 wk via daily intraperitoneal injections. Alterations of mesangial cell proliferation and extracellular matrix (ECM) production are believed to play predominant roles in the pathogenesis of progressive glomerulosclerosis which leads to ESRD (52, 53). In the process of tissue development and wound healing, TGF-β1 plays a crucial role in controlling ECM deposition and remodeling: TGF- β1 stimulates the synthesis of major components of ECM proteins, such as collagen and fibronectin (54-56). In diabetic kidneys, the overexpression of TGF- β1 is believed to be the major mediator responsible for early pathological changes of DN, including glomerular basement membrane thickening and mesangial matrix expansion (52, 55).

4-DAB treatment significantly ameliorated albuminuria and downregulated the expression of fibrogenic factor TGF-β1, subsequently reducing mesangial matrix protein production in diabetic mice kidney, without, however, changing serum glucose levels (Figures 5 and 6, Ref. 6). ADPR-cyclase was significantly activated, and cADPR levels were also increased in diabetic kidneys, which were prevented by 4-DAB treatment. On the other hand, plasma and kidney Ang II levels were elevated in both the diabetic and 4-DAB -treated diabetic mice group. This result suggests that 4-DAB affects only ADPR-cyclase activation, but not plasma and kidney Ang II levels in the diabetic experimental model. Furthermore, 4-DAB inhibited the phosphorylation of Akt and the NFAT3 nuclear translocation in the kidneys of the diabetic group. These findings indicate a crucial role of ADPR-cyclase signaling in the renal pathogenesis of diabetes and provide a therapeutic tool for the treatment of renal diseases.

6. Perspectives

A potent small-molecule inhibitor 4-DAB, that inhibits specifically the kidney ADPR-cyclase, has been discovered. The discovery of the specific inhibitor for the enzyme enables us to provide further evidence that there are ADPR-cyclases different from CD38. Benefits of the kidney ADPR-cyclase specific inhibitor are several folds: the use of 4-DAB may facilitate in the understanding of kidney functions involving the regulation of Ca^{2+} homeostasis; the inhibitor may help to understand the pathogenesis of the kidney; this compound can be the basis for the development of tissue specific inhibitors of ADPR-cyclases; and finally, the compound may be applied for therapeutic purposes for the prevention and management of human CKD. Furthermore, a similar strategy can be applied for the development of tissue specific inhibitors of ADPR-cyclases with the intent to intervene in other diseases, such as hypertension. For instance, the identification of an inhibitor for ADPR-cyclase of arterial smooth muscle cells can be a potential anti-hypertensive drug.

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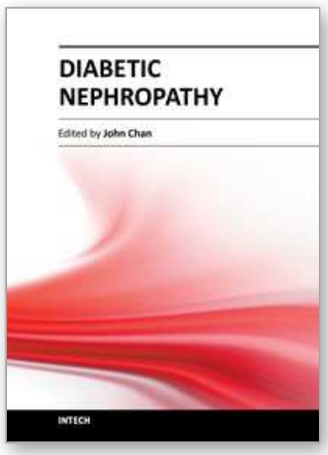

Diabetic Nephropathy

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Internationally renowned experts have provided data on their own studies, and discuss the relative usefulness of their work in relation to diabetic nephropathy. The first section describes the novel role of intrarenal renin-angiotensin-aldosterone system (RAAS) and oxidative stress in the development of diabetic nephropathy and discusses the current and novel pharmacological interventions in the treatment of diabetic nephropathy. The second section discusses other important contributors outside of the RAAS in the pathogenesis of diabetic nephropathy including AGE/RAGE, epithelial-mesenchymal-transition (EMT) and immune cytokines. Features: Provides novel information on various pathophysiological determinants in the development of diabetic nephropathy Provides novel information on various pharmacological interventions of diabetic nephropathy

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