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

Uh-Hyun Kim
Department of Biochemistry and the Institute of Cardiovascular Research, Chonbuk National University Medical School, Jeonju Republic of Korea

1. Introduction

ADP-ribosyl cyclases (ADPR-cyclases)/CD38 have emerged as effector 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 a 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\textsuperscript{2+}-mobilizing second messengers, cADPR and NAADP, from NAD\textsuperscript{+} and NADP\textsuperscript{+}, respectively (37-39). The second messenger, cADPR, increases intracellular Ca\textsuperscript{2+} concentration ([Ca\textsuperscript{2+}]\textsubscript{i}) through the release of Ca\textsuperscript{2+} from intracellular endoplasmic reticulum (ER) stores via ryanodine receptors and/or Ca\textsuperscript{2+} influx through plasma membrane Ca\textsuperscript{2+} channels (5, 39, 40, 41). The other second messenger, NAADP, increases intracellular Ca\textsuperscript{2+} concentration ([Ca\textsuperscript{2+}]\textsubscript{i}) through the release of Ca\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{2+} release from ER stores induces NAADP production by Rap1 activation via cAMP/Epac/PKA, resulting in the release of Ca\textsuperscript{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\textsuperscript{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\textsuperscript{2+} concentrations through a transient Ca\textsuperscript{2+} release via an inositol 1,4,5-trisphosphate receptor (IP\textsubscript{3}R) and a sustained Ca\textsuperscript{2+} influx via L-type Ca\textsuperscript{2+} channels. The sustained Ca\textsuperscript{2+} signal, but not the transient Ca\textsuperscript{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-\gamma1 (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 PLC-\gamma1, in turn causing a Ca\textsuperscript{2+} release by IP\textsubscript{3}R from ER, resulting in activation of ADPR-cyclase. Activation of ADPR-cyclase induces Ca\textsuperscript{2+} influx via L-type calcium channels, Akt phosphorylation, NFAT nuclear translocation, cell proliferation, and protein synthesis. 4-DAB abrogates the sustained Ca\textsuperscript{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](image-url)
Kidney ADP-Ribosyl Cyclase Inhibitors as a Therapeutic Tool for Diabetic Nephropathy

[³H]thymidine and [³H]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 e-ADPR from NGD$^+$ and e-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$^{2+}$], 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

www.intechopen.com
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. (adapted 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 $[\text{Ca}^{2+}]_{i}$, involving an initial peak rise followed by a sustained increase. Pre-treatment with 8-Br-cADPR inhibited only the sustained $\text{Ca}^{2+}$ rise. In contrast, 4-DAB did not show any effects on OKT3-mediated $\text{Ca}^{2+}$ 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.

7. Acknowledgments

This work was supported by the Korea Science and Engineering Foundation (National Research Laboratory Grant R0A-2007-000-20121-0). The author thanks Dr. Gabor Raffai and John Kang for critically reading the manuscript.
8. References

[1] Malavasi, F., Deaglio, S., Funaro, A., Ferrero, E., Horenstein, A. L., Ortolan, E., Vaisitti, T., and Aydin, S. (2008) Evolution and function of the ADP ribosyl cyclase/CD38 gene family in physiology and pathology. Physiol. Rev. 88:841 - 866

[2] Lee, HC (1997) Mechanisms of calcium signaling by cyclic ADP-ribose and NAADP. Physiol. Rev. 77:1133 - 1164

[3] Higashida H, Zhang JS, Hashi M, Shintaku M, Higashida C, and Takeda Y. (2000) Angiotensin II stimulates cyclic ADP-ribose formation in neonatal rat cardiac myocytes. Biochem J 352:197–202

[4] Kim SY, Gul R, Rah SY, Kim SH, Park SK, Im MJ, Kwon HJ, and Kim UH. (2008) Molecular mechanism of ADP-ribose cyclase activation in angiotensin II signaling in murine mesangial cells. Am J Physiol Renal Physiol 294: F982–F989

[5] Rah SY, Park KH, Han MK, Im MJ, and Kim UH. (2005) Activation of CD38 by interleukin-8 signaling regulates intracellular Ca²⁺ level and motility of lymphokine-activated killer cells. J Biol Chem 280: 2888–2895

[6] Kim SY, Park KH, Gul R, Jang KY, and Kim UH. (2009) Role of kidney ADP-ribose cyclase in diabetic nephropathy. Am J Physiol Renal Physiol 296: F291–F297

[7] USRD 2006 ADR/reference tables. Available at: http://www.usrds.org/reference_2006.htm 2008

[8] El-Nahas M (2005) The global challenge of chronic kidney disease. Kidney Int 68:2918–2929

[9] Vestra MD, Saller A, Mauer M, and Fioretto P. (2001) Role of mesangial expansion in the pathogenesis of diabetic nephropathy. J Nephrol 14: S51–S57

[10] Cooper ME. Interaction of metabolic and haemodynamic factors in mediating experimental diabetic nephropathy. (2001) Diabetologia 44: 1957–1972

[11] Coresh J, Astor BC, Greene T, Eknayan G, and Levey AS (2003) Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 41:1–12

[12] Harris RC. (2004) Diabetes and the kidney. In Cecil Textbook of Medicine, 22nd Ed. 750-753

[13] Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. (1993) N Engl J Med 329:977–986

[14] Parving H-H, Andersen ER, Smidt U, Hommel E, and Mathiesen E (1987) Antihypertensive treatment postpones endstage renal failure in diabetic nephropathy. Br Med J 294:1443–1447

[15] Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, Tuttle K, Douglas J, Hsueh W, and Sowers J (2000) Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis 36:646–661

[16] Lewis EJ, Hunsicker LG, and Bain RP. (1993) The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 329: 1456–1462
[17] Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, and Mustonen J. (2004) Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 351: 1952–1961

[18] Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, and Shahinfar S (2001) Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345:861–869

[19] Kostis JB, Shelton B, Gosselin G, Goulet C, Hood WB Jr, Kohn RM, Kubo SH, Schron E, Weiss MB, Willis PW 3rd, Young JB, and Probstfield J (1996) Adverse effects of enalapril in the Studies of Left Ventricular Dysfunction (SOLVD). SOLVD Investigators. Am Heart J 131:350–355

[20] Oparil S, Yarows SA, Patel S, Fang H, Zhang J, and Satlin A (2007) Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. Lancet 370:221–229

[21] Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, and Ideura T (2003) Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. Lancet 361:117–124

[22] Anderson PW, Do YS, and Hsueh WA. (1993) Angiotensin II causes mesangial cell hypertrophy. Hypertension 21: 29–35

[23] Feng Z, Wei C, Chen X, Wang J, Cheng H, Zhang X, Hong Q, Shi S, Fu B, and Wei R. (2006) Essential role of Ca^{2+} release channels in angiotensin II-induced Ca^{2+} oscillations and mesangial cell contraction. Kidney Int 70:130:138

[24] Kim S, and Iwao H. (2000) Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases. Pharmacol Rev 52: 11–34

[25] Guo DF, Sun YL, Hamet P, and Inagami T. (2001) The angiotensin II type 1 receptor and receptor-associated proteins. Cell Res 11: 165–180

[26] Seta K, Nanamori M, Modrall G, Neubig RR, and Sadoshima J. (2002) AT1 receptor mutant lacking heretotrimeric G protein coupling activates the Src-Ras-ERK pathway without nuclear translocation of ERKs. J Biol Chem 277: 9268–9277

[27] Howard M, Grimaldi JC, Bazan JF, Lund FE, Santos-Argumedo L, Parkhouse RME, Walseth TF, and Lee HC. (1993) Formation and hydrolysis of cyclic ADP-ribose catalyzed by lymphocyte antigen CD38. Science 262:1056–1059

[28] Jin D, Liu HX, Hirai H, Torashima T, Nagai T, Lopatina O, Shnayer NA, Yamada K, Noda M, Seike T, Fujita K, Takasawa S, Yokoyama S, Koizumi K, Shiraiishi Y, Tanaka S, Hashii M, Yoshihara T, Higashida K, Islam MS, Yamada N, Hayashi K, Naguchi N, Kato I, Okamoto H, Matsushima A, Salmina A, Muneseu T, Shimizu N, Mochida S, Asano M, and Higashida H. (2007) CD38 is critical for social behavior by regulating oxytocin secretion. Nature 446: 41–45

[29] Barbosa MT, Soares SM, Novak CM, Sinclair D, Levine JA, Aksoy P, and Chini EN. (2007) The enzyme CD38 (a NAD glycohydrolase, EC 3.2.2.5) is necessary for the development of diet-induced obesity. FASEB J 21:3629–3639

[30] Young GS, Choleris E, Lund FE, and Kirkland JB. Decreased cADPR and increased NAD^{+} in the Cd38^{-/-} mouse. Biochem Biophys Res Commun 346: 188–192, 2006.
[31] Reinherz EL, Kung PC, Goldstein G, Levey RH, and Schlossman SF. (1980) Discrete stages of human intrathymic differentiation: analysis of normal thymocytes and leukemic lymphoblasts of T-cell lineage. Proc Natl Acad Sci U S A 77: 1588-1592

[32] Koguma T, Takasawa S, Tohgo A, Karasawa T, Furuya Y, Yonekura H, and Okamoto H. (1994) Cloning and characterization of cDNA encoding rat ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase (homologue to human CD38) from islets of Langerhans. Biochim Biophys Acta 1223: 160-162

[33] Kramer G, Steiner G, Fodinger D, Fiebiger E, Rappersberger C, Binder S, Hofbauer J, and Marberger M. (1995) High expression of a CD38-like molecule in normal prostatic epithelium and its differential loss in benign and malignant disease. J Urol 154: 1636-1641

[34] Mizuguchi M, Otsuka N, Sato M, Ishii Y, Kon S, Yamada M, Nishina H, Katada T, and Ikeda K. (1995) Neuronal localization of CD38 antigen in the human brain. Brain Res 697: 235-240

[35] Verderio C, Bruzzone S, Zocchi E, Fedele E, Schenk U, De Flora A, and Matteoli M. (2001) Evidence of a role for cyclic ADP-ribose in calcium signalling and neurotransmitter release in cultured astrocytes. J Neurochem 78: 646-657

[36] States DJ, Walseth TF, and Lee HC. (1992) Similarities in amino acid sequences of Aplysia ADP-ribosyl cyclase and human lymphocyte antigen CD38. Trends Biochem Sci 17: 495

[37] Galione A, and Churchill GC. (2000) Cyclic ADP-ribose as a calcium-mobilizing messenger. Sci STKE 41: pe1

[38] Guse AH, Silva CP, Berg I, Skapenko AL, Weber K, Heyer P, Hohenegger M, Pitter BV, and Mayr GW. (1999) Regulation of calcium signaling in T lymphocytes by the second messenger cyclic ADP-ribose. Nature 398: 70-73

[39] Lee HC. (2001) Physiological functions of cyclic ADP-ribose and NAADP as calcium messengers. Annu Rev Pharmacol Toxicol 41: 317–345

[40] Partida-Sanchez S, Cockayne DA, Monard S, Jacobson EL, Oppenheimer N, Garvy B, Kusser K, Goodrich S, Howard M, Harmsen A, Randall TD, and Lund FE. (2001) Cyclic ADP-ribose production by CD38 regulates intracellular calcium release, extracellular calcium influx and chemotaxis in neutrophils and is required for bacterial clearance in vivo. Nat Med 7:1209-1216

[41] Higashida H, Salmina AB, Olovyanikova RY, Hashii M, Yokoyama S, Koizumi K, Jin D, Liu HX, Lopatina O, Amina S, Islam MS, Huang JJ, and Noda M. (2007) Cyclic ADP-ribose as a universal calcium signal molecule in the nervous system. Neurochem Int 51: 192–199

[42] Calcraft, Pj, Ruas, M., Pan, Z., Cheng, X., Arredouani, A., Hao, X., Tang, J., Rietdorf, K., Teboul, L., Chuang, KT, Lin, P., Xiao, R., Wang, C., Zhu, Y., Lin, Y., Wyatt, CN, Parrington, J., Ma, J., Evans, AM, Galione, A., and Zhu, MX (2009) NAADP mobilizes calcium from acidic organelles through two-pore channels. Nature 459, 596 - 600

[43] Kim B.-J., Park K., Yim C., Takasawa S., Okamoto H., Im M. , and Kim UH. (2008) Generation of nicotinic acid adenine dinucleotide phosphate and cyclic ADP-ribose by glucagon-like peptide-1 evokes Ca2+ signal that is essential for insulin secretion in mouse pancreatic islets. Diabetes 57, 868–878
[44] Rah SY, Mushtaq M, Nam TS, Kim SH, and Kim UH. (2010) Generation of Cyclic ADP-ribose and Nicotinic Acid Adenine Dinucleotide Phosphate by CD38 for Ca\textsuperscript{2+} Signaling in Interleukin-8-treated Lymphokine-activated Killer Cells. J Biol Chem 285: 21877–21887

[45] Ceni C, Muller-Steffner H, Lund F, Pochon N, Schweitzer A, De Waard M, Schuber F, Villaz M, and Moutin MJ. (2003) Evidence for an intracellular ADP-ribosyl cyclase/NAD\textsuperscript{+}-glycohydrolase in brain from CD38- deficient mice. J Biol Chem 278: 40670–40678

[46] de Toledo FG, Cheng J, Liang M, Chini EN, and Dousa TP. (2000) ADP-ribosyl cyclase in rat vascular smooth muscle cells: properties and regulation. Circ Res 86: 1193–1199

[47] Nam TS, Choi SH, Rah SY, Kim SY, Jang W, Im MJ, Kwon HJ, and Kim UH. (2006) Discovery of a small-molecule inhibitor for kidney ADP-ribosyl cyclase: implication for intracellular calcium signal mediated by cyclic ADP-ribose. Exp Mol Med 38: 718–726

[48] Gul R, Kim SY, Park KH, Kim BJ, Kim SJ, Im MJ, and Kim UH. (2008) A novel signaling pathway of ADP-ribosyl cyclase activation by angiotensin II in adult rat cardiomyocytes. Am J Physiol Heart Circ Physiol 295:H77–H88

[49] Rah SY, Park KH, Nam TS, Kim SJ, Kim H, Im MJ, and Kim UH. (2007) Association of CD38 with nonmuscle myosin heavy chain IIA and Lck is essential for the internalization and activation of CD38. J Biol Chem 282: 5653–5660

[50] Kim SY, Cho BH, and Kim UH. (2010) CD38-mediated Ca\textsuperscript{2+} Signaling Contributes to Angiotensin II-induced Activation of Hepatic Stellate Cells. J Biol Chem 285: 576–582

[51] Zubiaur M, Izquierdo M, Terhorst C, Malavasi F, and Sancho J. (1997) CD38 ligation results in activation of the Raf-1/mitogen-activated protein kinase and the CD3-zeta/zeta-associated protein-70 signaling pathways in Jurkat T lymphocytes. J Immunol 159: 193–205

[52] Liu Y. (2006) Renal fibrosis: new insights into the pathogenesis and therapeutics. Kidney Int 69: 213–217

[53] Ruiz-Torres MP, Lopez-Ongil S, Grier M, Diez-Marques ML, Rodriguez-Puyol M, and Rodriguez-Puyol D. (2005) The accumulation of extracellular matrix in the kidney: consequences on cellular function. J Nephrol 18:334–340.

[54] Chen S, Hong SW, Iglesias-de la Cruz MC, Isono M, Casaretto A, and Ziyadeh FN. (2001) The key role of the transforming growth factor-beta system in the pathogenesis of diabetic nephropathy. Renal Fail 23: 471–481

[55] Mezzano SA, Ortega MR, and Egidio J. (2001) Angiotensin II and renal fibrosis. Hypertension 38: 635–638

[56] Ziyadeh FN, Sharma K, Erickson M, and Wolf G. (1994) Stimulation of collagen gene expression and protein synthesis in murine mesangial cells by high glucose is mediated by autocrine activation of transforming growth factor beta. J Clin Invest 93: 536–542
Diabetic Nephropathy
Edited by Dr. John Chan

ISBN 978-953-51-0543-5
Hard cover, 166 pages
Publisher InTech
Published online 20, April, 2012
Published in print edition April, 2012

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

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Uh-Hyun Kim (2012). Kidney ADP-Ribosyl Cyclase Inhibitors as a Therapeutic Tool for Diabetic Nephropathy, Diabetic Nephropathy, Dr. John Chan (Ed.), ISBN: 978-953-51-0543-5, InTech, Available from: http://www.intechopen.com/books/diabetic-nephropathy/kidney-adp-ribosyl-cyclase-inhibitors-as-a-therapeutic-tool-for-diabetic-nephropathy-