Oxidative stress in the pathogenesis of diabetic nephropathy

N Agrawal, S Singh, N Singh, S Kalra, G Srivastava

Citation

N Agrawal, S Singh, N Singh, S Kalra, G Srivastava. *Oxidative stress in the pathogenesis of diabetic nephropathy*. The Internet Journal of Family Practice. 2009 Volume 9 Number 1.

Abstract

Nephropathy is an important chronic microvascular complication of diabetes, which has multiple pathophysiologic mechanisms. This review discusses the various oxidative and gluco-oxidative reactions which lead to renal damage in people with diabetes.

INTRODUCTION

Diabetic nephropathy is the leading cause of end stage renal diseases, and is a significant cause of morbidity and mortality in persons with diabetes.

While multiple pathophysiologic mechanisms contribute to the development of diabetic nephropathy, there is ample evidence to implicate oxidative stress and gluco-oxidative stress in the pathogenesis of this complication. Oxidative stress is created by various molecules, such as reactive oxygen species (ROS) and reactive dicarbonyl species, which result in renal damage through different mechanisms.

The sources of oxidative stress, i.e. ROS and reactive dicarbonyl in diabetes have been discussed earlier (1). This review focuses on the actions and pathways that these species take to create renal damage in diabetes.

REDOX REACTIONS

Diabetes nephropathy is characterized by glomerular mesangial expansion, due to deposition of extracellular matrix (2). This occurs because of both increased synthesis and reduced degradation of extracellular matrix proteins (ECMs), and is mediated by the high concentrations of glucose, Ang II, extracellular AGE proteins and a thromboxane analogue. These factors have been studied both in vitro and in vivo. (1)

All these factors stimulate cell signaling pathways which increase transforming growth factor-β (TGF-β) in the matrix protein. This is done via ROS generation. ROS is derived from NADPH oxidase activation, and also from the mitochondria (3). NADPH oxidase is activated by activation of protein kinase C (3), and vice versa (4).

ROS generation has been shown to increase in mitochondria in response to hyperglycemia, Ang II and AGE (3). Inhibitions of NADPH oxidase suppress the increase in TGF-β_1 and extracellular matrix proteins (3). The same phenomenon is noted with inhibitors of mitochondrial electron transport, and with a variety of exogenous antioxidants (5, 6).

Antioxidants also inhibit the activation of nuclear factor-KB and specificity factor 1, and inhibit the increase in monocyte chemoattractant protein-1 or PAI-1 seen with hyperglycemia, Ang II, AGE as well as thromboxane A2 (7).

Through enhanced production of ROS, transition from renal tubular epithelial cells to mesenchymal cells has been demonstrated (8). This process leads to interstitial fibrosis. In endothelial cells, mitochondrial ROS increases as a response to hyperglycemia. Superoxide suppresses GAPDH, activates PKC, and increases AGE formation, thus causing tissue damage.

Benfotiamine, which is a lipid-soluble derivatives of thiamine, has been shown to suppress the activation of PKC, hexosamine pathway, NF-KB and AGE formation (9) seen with hyperglycemia. It has also been shown to suppress retinopathy development in diabetic rats (9), but a similar effect on renal tissue has not been demonstrated so far. ,

Hemodynamic, functional and structural changes in diabetic nephropathy have been linked to alterations in NO signaling. (10)

Synthesis of both NO and superoxide is increased in diabetes (11), and this imbalance alters the hemodynamics in the

kidney.

Interaction of NO by superoxide leads to vasoconstriction, due to loss of its vasodilator action. Excess superoxide per se causes renal vasoconstriction (12) while its conversion to H2O2 leads to vasodilation (13).

Because of these varied actions, the net effect may be different at different stages of the disease. In early diabetic nephropathy, glonerular hyperfiltration and renal vasodilation may occur because of increased NO bioavailability due to enhanced NO production by eNOS. (14)

Glomerular mesangial cells and extracellular matrix proteins proliferate in response to hyperglycemia, Ang II and other factors via NO. NO has an antiproliferative effect on this reaction, via PKC and TGF- . Antioxidants have therefore been used to increase NO suppression of mesangial cell growth and synthesis of extracellular matrix protein in hyperglycemia.

NO and superoxide react to form peroxynitrite, which alters protein structure and function, and cause cell injury. (15)

If superoxide concentrations are reduced, there is less peroxynitrite production, and this is renoprotective. (16)

THERAPEUTIC IMPLICATIONS

Oxidative stress is an important patholgenetic factor in diabetic nephropathy. It stands to reason, therefore, that drugs which reduce oxidative stress may provide renoprotective.

This effect has been seen with angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), both of which are used as antihypertensive and renoprotective/vasculoprotective agents.

Specific inhibitors of oxidative stress have also been tried in animals and humans. These include aminoguanidine, which inhibits AGE, and prevents albuminuria. (17) Soluble blockers of RAGE have also been shown to reduce renal damage. (18)

Antioxidants such as vitamin E and C, lipoic acid, and taurine have shown beneficial effects on renal function (1) in short term trials.

While non of the existing antioxidants has shown therapeutic promise over long term, animal studies with the SOD mimetic drug called tempol have shown beneficial results in reversing systemic hypertension and reducing GFR. (19) Future studies on this class of molecules may lead to a break through in the management of diabetic nephropathy with antioxidants.

CONCLUSION

Oxidative stress is an important pathogenetic factor in the causation of diabetic nephropathy. Therapeutic strategies which reduce the burden of oxidative stress may be useful in managing this condition.

References

1. De Rubertis FR, Craven PA. Oxidative and glycooxidative stress in diabetic nephropathy. In: Cortes P, Mogensen CE. Contemporary Diabetes: The Diabetic Kidney. Humana, Totowa, NJ. 2006; PP 151-172.
2. Caramori ML, Mauer M. Diabetes and nephropathy. Cur Opin Nephrol Hypertens 2003; 12(3): 273-282.
3. Lee HB, Yu M-R, Yang Y, Jiang Z, Ha H. Reactive oxygen species-regulated signaling pathways in diabetes nephropathy. J Am Soc Nephrol 2003; 14:S245.
4. Hua H, Munk S, Goldberg H, Fantus IG, Whiteside CI. High glucose-suppressed endothelin-1 Ca2+ signaling via NADPH oxidase and diacylglycerol-sensitive protein kinase C isozymes in mesangial cells. J Biol Chem 2003; 278:33, 951-33,951-33,962.
5. Craven P, Phillips S, Melhem M, Liachenko J, DeRubertis FR. Overexpression of Mn2+ superoxide dismutase suppresses increases in collagen accumulation induced by culture of mesangial cells in high media glucose. Metabolism 2001; 50:1043-1048.
6. Studer RK, Craven PA, DeRubertis FR. Antioxidant inhibition of protein kinase C-signaled increases in transforming growth factor-beta in mesangial cells. Metabolism 1997; 46:918-925.
7. Lee HB, Yu M, Yang Y, Jiang Z, Ha H. Reactive oxygen species-regulated signaling pathways in diabetic nephropathy. J Am Soc Nephrol 2003; 14:S241-S245.
8. Yang Y, Ha H, Lee HB. Role of reactive oxygen species in TGF induced epithelial to mesenchymal transition. Nephrol Dial Transplant 2003; 18(4):300.
9. Hammes HP, Du X, Edelstein D, et al. Benfotiamine blocks three major pathways of hypoglycemic damage and prevents experimental diabetic retinopathy. Nat Med 2003;9:294-299.
10. Komers R, Anderson S. Paradoxes of nitric oxide in the diabetic kidney. Am J Physiol Renal Fluid, Electrolyte Physiol 2003;284:1121-1137.
11. Craven PA, Melhem MF, Phillips SL, DeRubertis FR. Overexpression of Cu2+/Zn2+ superoxide dismutase protects against early diabetes glomerular injury in transgenic mice. Diabetes 2001;50:2114-2125.
12. Schnackenberg CG. Physiological and pathophysiologic roles of oxygen radicals in the renal microvasculature. Am J Physiol Regul Integrat Comp Physiol 2002; 282:R335-R342.
13. Burke TM, Wolin MS. Hydrogen peroxide elicits pulmonary arterial relaxation and guanylate cyclase activation. Am J Physiol 1987;252:H721-H732.
14. Bank N, Aynedijan HS. Role of EDRF in diabetic renal hyperfiltration. Kidney Int 1993; 43:1306-1312.
15. Beckman JS, Koppenol WH, Nitric oxide, superoxide and peroxynitrite the good, the bad and the ugly. Am J Physiol 1996; 271:C1424-C1437.
16. DeRubertis FR, Craven PA, Melhem MF, Salah EM.

Attenuation of renal injury in db/db mice overexpressing superoxide dismutase: evidence for reduced superoxide-nitric oxide interaction. Diabetes 2004; 53:762-768.
17. Soulis-Liparota T, Cooper M, Papazoglou D, Clarke B, Jerums G. Retardation by aminoguanidine of development of albulinuria, mesangial expansion and tissue fluorescence in streptozotocin induced diabetic rat. Diabetes 1999; 40:1328-1334.
18. Park L, Raman KG, Lee KJ, et al. Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. Nat Med 1998; 4:1025-1031.
19. Zorov DB, Filburn CR, Klotz LO, Zweier JL, Sollott SJ. Reactive oxygen species (ROS)-included ROS release: a new phenomenon accompanying induction of the mitochondrial permeability transition in cardiac myocytes. J Exp Med 2000; 192:1001-1014.

Author Information

Navneet Agrawal
Dept of Medicine, GR Medical College, Gwalior, India

Sanjeev Kumar Singh
Dept of Biochemistry, GR Medical College, Gwalior, India

Neelima Singh
Dept of Biochemistry, GR Medical College, Gwalior, India

Sanjay Kalra
B.R.I.D.E., Karnal, India

Gautam Srivastava
B.R.I.D.E., Karnal, India