Gluco oxidative stress in the diabetic kidney

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Abstract

This review deals with the effect of hypoglycemia and oxidative stress on renal tissue in diabetes. It focuses on the effect of advanced glycation endproducts (AGEs). It covers the potential utility of this pathway as a future therapeutic target for prevention and management of diabetic nephropathy.

INTRODUCTION

AGEs, generated in hyperglycemic conditions, by non enzymatic glycation, protein oxidation and lipid oxidation, including pentosidine, carboxymethyl lysine AGEs, and pyrallines, are well known to cause diabetic complications. (1, 2)

AGEs can be measured in tissue as well as serum or plasma, and rise in parallel with hyperglycemia (because of increased formation), and decline in renal function (due to reduction in renal clearance).

AGEs react with various receptors including scavenger receptors including scavenger receptor type A, CD 36, galectin-3, and RAGE. RAGE is a member of the immunoglobulin superfamily of cell-surface molecules, and activities intracellular signal transduction pathways to achieve the effects of AGE.

RAGE is expressed to a greater degree in diabetic kidneys, at the glomerular visceral epithelial cell (podocyte). (3)

RAGE is a receptor for other ligands such as 5100/calgranulins (100), amphoterin [high-mobility group box-1 (HMGB 1) protein], amyloid-□ peptide, □-sheet fibrils and Mac-1, all of which are pro-inflammatory molecules.

BLOCKADE OF RAGE

Soluble RAGE (RAGE), or neutralizing antibody to RAGE have been used to block the ligand-RAGE axis, in animal experiments. Blockade is also simulated in mouse mesangial cells producing limited RAGE-specific ribozymes. (1)

In these models, improvements in kidney morphology and biochemical parameters have been noted with RAGE antagonism. These animal experiments emphasize the importance of gluco oxidation via the RAGE axis in the pathogenesis of diabetic nephropathy.

Genetic models have also been studied to explore the role of RAGE. While transgenic mice with other expression of RAGE demonstrate increased nephromegaly, glomerular hypertrophy, mesangial expansion, advanced glomerulosclerosis, increased albuminuria and serum creatinine than RAGE transgene-negative mice. Administration of OPB-9195, an AGE inhibitor, was able to prevent nephropathy in these mice (3).

Similar studies have also demonstrated increased kidney/body weight ratio, and increased renal cortex expression of VEGF antigen and TGF-□ transcription, in RAGE-expressing mice with diabetes, as compared to RAGE-null mice. (4)

DOWNSTREAM EFFECTS OF RAGE SIGNALING

RAGE activation leads to a large number of diverse signaling pathways, which vary according to cell type and duration of stimulation.

RAGE signaling triggers recruitment of p 21 ras, erk ½ (p44/p42) MAP kinases, p38 and SAPK/JNK MAP kinases, rho GTPases, phosphoinositol-3 kinase, and the JAK/STAT pathway, while activating transcription factors such as nuclear factor-kB and CREB (1).

RAGE signalling is linked to TGF-□-Smad signalling and to angiotensin II. The angiotensin receptor blocker, candesartan, is able to reduce AGE-induced phosphorylation of Smad 2 and TGF-□ inducible promotor activity. (5)

RAGE activation also leads to p21 waf expression, collagen production, and epithelial-myofibroblast transdifferentiation, which may explain a potential role for RAGE in the progression of tubulo interstitial disease. (7, 8)

THERAPEUTIC IMPLICATIONS

AGE and RAGE both have been used as therapeutic targets for prevention of diabetic nephropathy.

The AGE inhibitor aminoguanidine (pimagedine) has been used in human subjects with type 1 diabetes. (9) Though the drug increased the time taken to double serum creatinine, reduced the rate of decline of glomerular filtration rate, and reduced 24 hour proteinuria, three subjects developed glomerulonephritis.

Agents such as ALT-711, an AGE cross link breakers, have been assessed in animal models of diabetes nephropathy, and in elderly humans with vascular stiffening. Antagonists such as pyridoxamine and LR-90 have been studied in animals. (1)

While no anti-AGE drug has reached the clinical stage, the AGE hypothesis is strong enough for researchers to continue working on this pathway.

RAGE antagonists have not been tested in human trials, but pre-clinical studies support the concept of targeting RAGE in order to prevent or slow diabetic nephropathy.

Researchers have also studied combinations of perindopril with aminoguanidine in rats, finding superior protective effects. (10)

Others have reported that ramipril and valsartan are able to reduce AGE formation independently. (10, 11)

These findings encourage one to believe that AGE or RAGE antagonism may emerge as an important therapeutic modality in future.

GLYCEMIC MEMORY OR GLUCO OXIDATIVE MEMORY

Research has shown that intensive glucose control is linked with better renoprotection, even years after intensive control, in spite of gradually worsening HbA1c, in type 1 diabetes.

This glycemic memory may be mediated through AGE-RAGE interaction, and may more appropriately be termed ‘gluco-oxidative memory’.

CONCLUSION

This brief review has discussed the functions of RAGE, and its potential as a therapeutic strategy in managing diabetic nephropathy. It has tried to simplify a difficult aspect of pathophysiology of diabetes/diabetic nephropathy, to enable family practitioners understand the advances taking place in this field of science.

References

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