Oxidative Stress Promotes Hypertension and Albuminuria During the Autoimmune Disease Systemic Lupus Erythematosus

To the Editor:

We read with interest the recent article by Mathis et al., which shows that antioxidant therapy reduces blood pressure and albuminuria in an established model of systemic lupus erythematosus (SLE) with associated hypertension. The authors also suggest that, although therapy does not alter SLE disease progression, it does reduce renal oxidative stress. We raise several issues.

Reducing proteinuria is a key goal in chronic kidney disease management in the clinic, and this is best achieved by reducing blood pressure. Thus, the reduction in albuminuria seen here with antioxidant therapy may, in part, be explained by the fall in blood pressure. In the abstract, the authors suggest that this fall in albuminuria reflects a reduction in “renal injury.” We argue that this is an overinterpretation of the data. Generally, and in particular in SLE with associated nephritis, assessment of renal injury is best done using histology. Indeed, this group has recently published in Hypertension and shown that, using this same model of SLE, treatment with the anti-inflammatory agent etanercept reduced blood pressure and albuminuria—similar to the results of the current study—but additionally reduced glomerulosclerosis and glomerular inflammatory cell infiltration. In the current study, given that the authors show the histological effects of antioxidant treatment on renal oxidative stress, it would have been of great interest to see the effects of therapy on glomerular injury.

Although the authors state that antioxidant treatment did not alter SLE disease progression because the plasma levels of double-stranded DNA autoantibodies did not change, it should be recognized that these autoantibodies are more a marker of SLE disease activity (and, in isolation, a relatively poor marker at that), and disease progression would once again have been better assessed with renal histology.

Although the authors state that antioxidant therapy reduces renal oxidative stress, there are only modest data in support of this. In a small number of animals (n=3–4), of the 4 nitrosylated proteins assessed, only 1 showed increased nitrosylation in the SLE animals compared with controls. In favor of the authors’ statement, this protein did not show increased nitrosylation with antioxidant treatment. Interestingly, although there were no differences in renal cortical or urinary hydrogen peroxide levels between control and vehicle-treated SLE animals, antioxidant therapy did reduce urinary hydrogen peroxide concentrations in SLE (but not control) animals. A previous article in Hypertension may provide some mechanistic insights into this. Here, in the Dahl salt-sensitive rat with heart failure, subpressor doses of an angiotensin-converting enzyme inhibitor reduced renal angiotensin II and upregulated the renal NO system. Of relevance, there were reductions in NADPH oxidase expression, urinary hydrogen peroxide, albuminuria, and glomerulosclerosis. Thus, the effects of antioxidant therapy in the current study may partly be explained by changes in renal vasoconstrictor-vasodilator balance, and this would be an interesting avenue for future research.

Disclosures

None.

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