Effects of RAGE blockade on inflammation, oxidative stress and nitric oxide bioavailability in transgenic sickle mice

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Sickle cell disease (SCD) is characterized by increased plasma levels of advanced glycation end products (AGEs). Under oxidative conditions, AGEs are generated by non-enzymatic glycation and oxidation of proteins and lipids that amplify oxidative stress when binding to their receptor (RAGE). The aim of this study was to characterize the effects of RAGE blockade with a specific antagonist (RAP) in a transgenic mouse model of SCD (Townes). Eight week-old AA (normal), AS (sickle cell trait) and SS (homozygous SCD) mice were treated intraperitoneally with RAP or vehicle. After 3 weeks of treatment, red blood cell count and hematocrit were significantly higher in RAP-treated SS mice. Reticulocyte count was lower in RAP-SS compared to their vehicle-treated littermates. RAP-treated SS mice had decreased TNF-\textalpha~ mRNA expression in heart and kidney and decreased IL-1\textbeta~ mRNA expression in lung. In liver, TNF-\textalpha and IL-1\textbeta mRNA expression was higher in vehicle-treated SS compared to AA mice while the same difference was not significant between RAP-treated SS and AA mice. The lower glutathione peroxidase activity in RAP-SS kidney compared to vehicle SS mice suggest reduced ROS production. Finally, eNOS mRNA expression was increased in kidney of RAP-SS and correlated with eNOS protein expression suggesting higher production of nitric oxide (NO) in RAP-SS mice. These results suggest that RAGE blockade may reduce inflammation, oxidative stress and increase NO bioavailability in sickle mice.