ROSUVASTATIN PREVENTS PROGRESSIVE KIDNEY INFLAMMATION AND FIBROSIS IN STROKE-PRONE RATS BY MODULATING THE PLASMINOGEN/PLASMIN SYSTEM AND THE METALLOPROTEASES EXPRESSION

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Background: The incidence of chronic renal diseases is increasing worldwide, and there is a great need to identify therapies capable of arresting or reducing disease progression. The current treatment of chronic nephropathies is limited to angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, but there is growing clinical and experimental evidence that statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) could play a therapeutic role. Salt-loaded spontaneously hypertensive stroke-prone rats (SHRSP) show progressive increases in blood pressure and proteinuria and accumulate acute-phase proteins in body fluids, modelling events during renal damage. SHRSP offer an opportunity to disentangle the complex pathological processes occurring during the development of renal failure, and to test the effects of potentially renoprotective therapies. The aim of this study was to assess the pathological events occurring in the kidney of SHRSP over time and investigated the effects of the lipophilic simvastatin and the hydrophilic rosuvastatin on these events. **Methods:** Fifty six-week-old SHRSPs were fed a high-salt diet and randomly divided into three groups for oral treatment with vehicle, rosuvastatin or simvastatin at the dose of 10 mg/kg/day (n=15 each group). Animals were euthanized at different time of proteinuria and the kidneys collected for histological evaluation and profile of the fibrinolytic and metalloprotease systems. For comparison, baseline kidneys from SHRSP (n=6) were collected at the start of the high-salt diet. **Results**: Kidneys of male SHRSP euthanized at different stages of proteinuria showed progressive inflammatory cell infiltration, accumulation of alpha-smooth muscle actin-positive cells, degenerative changes in podocytes, and severe fibrosis. These were accompanied by an imbalance in the plasminogen/plasmin and metalloprotease systems characterised by the increased renal expression of PAI-1, tPA and uPA; the net result was an increase in plasmin and MMP-2 and a reduction in MMP-9 activity. Chronic treatment with the hydrophilic rosuvastatin had renoprotective effects in terms of morphology and inflammation and prevented the changes in plasmin, MMP-2 and MMP-9 activity. These effects were independent of the changes in blood pressure and plasma lipid levels. Treatment with the lipophilic simvastatin was not renoprotective. **Conclusion**: These data suggest that some statins, with hydrophilic properties, may have potential utility as a therapeutic option in renal diseases that are characterised by inflammation and fibrosis.