Accelerated Renal Senescent Phenotype in the AS/AGU Rat: A Novel In-vivo Model

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OBJECTIVES

The mutant rat sub-strain (AS/AGU) arose spontaneously as a result of a specific single gene mutation (PKCγ) in a colony of Albino Swiss (AS) rats.

It was initially characterised as giving rise to a parkinsonian movement disorder due to loss of dopaminergic neurons from the substantia nigra pars compacta.¹

The strain was demonstrated to display accelerated bio-ageing in the kidney (Wright et al: unpublished data) and we have subsequently performed glomerular filtration (GFR) and biochemical studies to phenotypically characterise this model.

METHODS

0.2% w/v Flourescein Isothiocyanate Inulin (FITC-Inulin) was used for GFR experiments by constant infusion through a central vein under general anaesthesia.

Measurements of fluorescence in the urine of each kidney and plasma at equilibrium provided quantitative data on the filtration process across the glomerulus, which was then calculated according to the equation:

\[ \text{GFR} = \frac{\text{Urine FITC fluorescence} \times \text{urine flow rate}}{\text{Plasma FITC fluorescence}} \]

(standardised to 100 grams body weight)

Laboratory biochemical analysis was performed on separated plasma and urinary samples

RESULTS

A - There was a proportional increase in GFR with increasing age of the animal (n=24, p=<0.001)

B - Standardised GFR/100gr body weight (bw) showed a parallel decline with age, mutant rats showing persistently lower GFR/100gr bw. The difference between the two groups in the experimental cohort approached significance (n=24, p=0.065)

C - A significant difference in GFR/100gr body weight was observed between AS and AS/AGU female rats (n=1, p=0.028)

D - Biochemical analysis showed a significant difference in both sodium and urea concentrations between the strains (n=61), with mutant AS/AGU having higher mean urea concentrations (8.67mmol/L vs 7.23mmol/L, p=0.009) and lower mean sodium concentrations (144.7mmol/L vs 146.9mmol/L, p=0.023)

CONCLUSIONS

This strain is a unique and useful model of human diseases of ageing and organ dysfunction, in particular for renal dysfunction and transplant related pathologies.

It is postulated that the PKCγ mutation impairs the sodium-urea counter transporter in the rat inner-medullary collecting duct and in conjunction with the difference in GFR between both strains, confirms the premature senescent genotype of the mutant AS/AGU strain.

This provides a promising and sound basis for future transplant-related scientific research.

References
