

The effect of P2X7 antagonism on nephrotoxic nephritis

Dr Maria Prendecki¹, Dr Stephen McAdoo¹, Dr Tabitha Turner-Stokes¹, Mrs Gurjeet Banghal¹, Dr Kevin Willard¹, Dr Jacques Behmoaras¹, Prof Tim Aitman¹, Prof H.Terence Cook¹, Prof Robert Unwin², Prof Charles Pusey¹, Prof Fred Tam¹

¹Imperial College, London, United Kingdom, ²UCL Centre for Nephrology, London, United Kingdom

Introduction

P2X7 is an inotropic receptor for extracellular ATP which is thought to be important in inflammation and fibrosis. We have described a novel P2X7 knockout rat which seems to be a true knockout but is not protected from experimental models of glomerulonephritis or vasculitis. Here we have used two small molecule antagonists of P2X7 to further define a role for P2X7 in glomerulonephritis

Methods

Nephrotoxic nephritis (NTN) was induced in male WKY or P2X7 KO (on a WKY background) rats using a single IV injection of nephrotoxic serum. Animals were treated with one of two distinct P2X7 antagonists from day 1 after immunisation and were sacrificed at day 7. Antagonist 1- A438079 was administered twice a day by intraperitoneal injection (IP) and based on a previous study using this antagonist in NTN a dose of 275µmol/kg was used. Antagonist 2- AZ11657312 was administered twice daily by oral gavage at a dose of 60mg/kg based on information provided by Astra Zeneca. Control animals received equivalent sterile water IP or by oral gavage respectively. Disease severity was assessed at day 7.

Results

A438079 significantly reduced disease severity in both P2X7 KO and WKY WT rats. Proteinuria was almost completely abolished in treated rats and renal function was improved as measured by urea or urea clearance. Severity of glomerular injury by light microscopy was significantly improved with profound cellular infiltrate and extensive fibrinoid necrosis seen in both groups of vehicle treated rats and near normal glomerular histology in antagonist treated rats. The results from this experiment are shown in Figure 1.

AZ11657312 had no effect on disease severity in either P2X7 KO or WK WT with similar degrees of urinary abnormalities, glomerular injury and glomerular leucocyte infiltration in all groups (data not shown).

Discussion

A438079 has a significant effect on severity of NTN but was equally effective in WKY WT and P2X7 KO rats, implying it may be mediating its effects via off target effects. The dose used in our in vivo experiments was similar to other published studies including the initial characterisation of this antagonist, but was a 10 times higher dose than that used to generate PK data in rats. AZ11657312 had no effect on severity of NTN implying it is likely to be a more selective inhibitor of P2X7 at the dose used, and that P2X7 antagonism is not effective for the treatment of nephrotoxic nephritis.