SP062

EFFECTS OF JNK INHIBITOR ON PUROMYCIN AMINONUCLEOSIDE-INDUCED NEPHROPATHY IN RATS

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Introduction

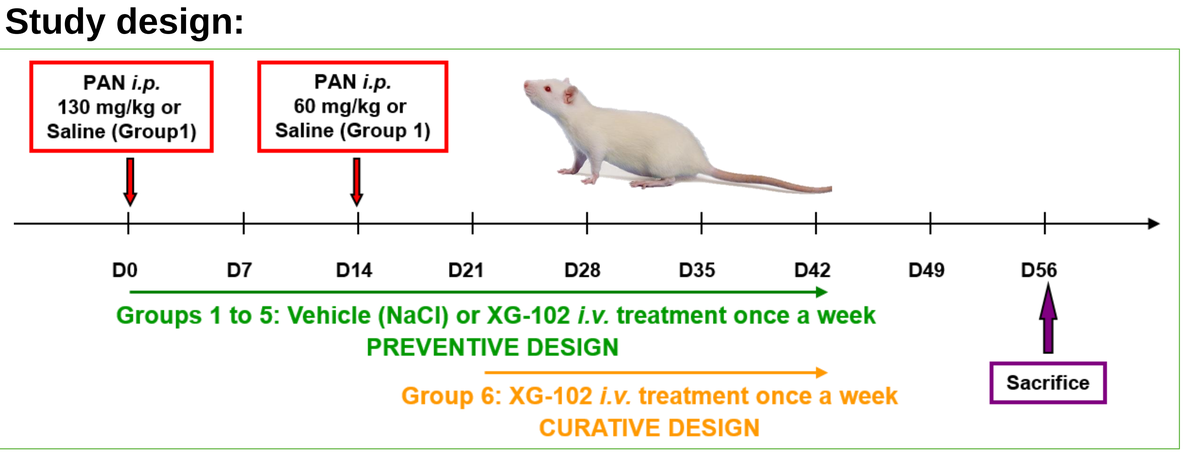
+ Puromycin aminonucleoside (PAN) is a podocyte toxin inducing a loss and fusion of podocytes foot processes.
+ Repeated PAN injections in rats[1] lead to a direct DNA damage via the production of reactive oxygen species (ROS) and tissue damages, including glomerulosclerosis and interstitial fibrosis[2].
+ c-Jun N-terminal kinase (JNK) is a stress-activated protein kinase which can be induced by various stimuli including ROS and pro-inflammatory cytokines[3].
+ JNK activation seems to play an important role in the development and progression of kidney diseases[3].

Objective

The aim of this study was to evaluate the preventive and/or curative effect of a JNK inhibitor (XG-102) in a chronic rat model of puromycine aminonucleoside (PAN)-induced nephropathy.

Methods

+ **Animals:** rat, Wistar, males (15/group).
+ **Nephropathy induction:** PAN was administered *i.p.* at day 0 (130 mg/kg) and at day 14 (60 mg/kg).
+ **Study design:**



+ **Experimental groups:**

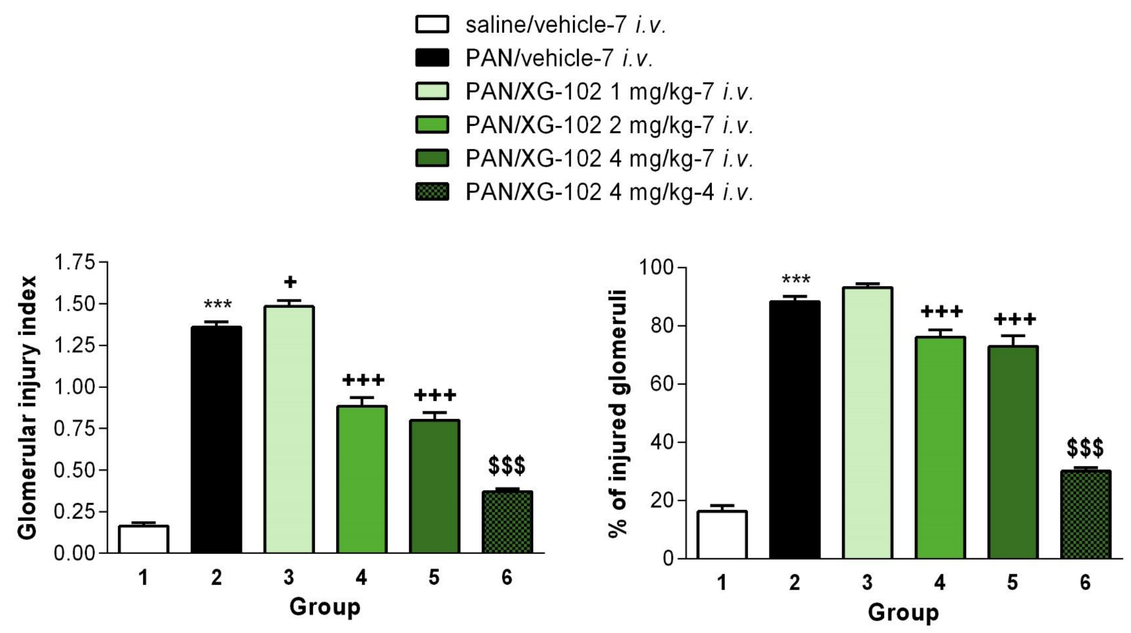
Group	PAN *(i.p.)*	Treatment *(i.v)*	Number of *i.v.* administrations	n
1	no	vehicle	7	15
2	yes	vehicle	7	15
3	yes	XG-102 (1 mg/kg)	7	15
4	yes	XG-102 (2 mg/kg)	7	15
5	yes	XG-102 (4 mg/kg)	7	15
6	yes	XG-102 (4 mg/kg)	4	15

+ **Histology:** glomerular damages evaluation by score system on Periodic Acid Shiff (PAS) and hematoxilin/eosin (HE) staining of kidney sections.

Results

Effect of XG-102 on PAN-induced glomerular damages

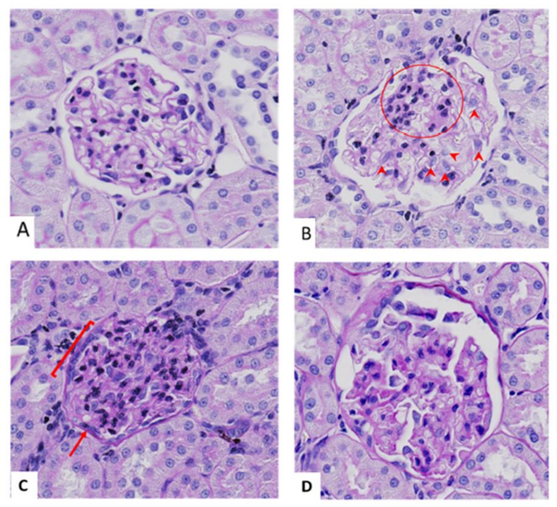
Quantification of glomerular damages



***P<0.001 *versus* Group 1 using unpaired Student *t*-test
+ P<0.05; +++P<0.001*versus* Group 2 using one-way ANOVA followed by followed by Newman-Keuls test
$$$ P<0.001 versus Group 2 using unpaired Student *t*-test

XG-102 significantly reduced PAN-induced glomerulosclerosis in term of both severity of lesions (glomerular injury score) and incidence (percentage of injured glomeruli). These effects are more important using curative treatment schedule (Group 6).

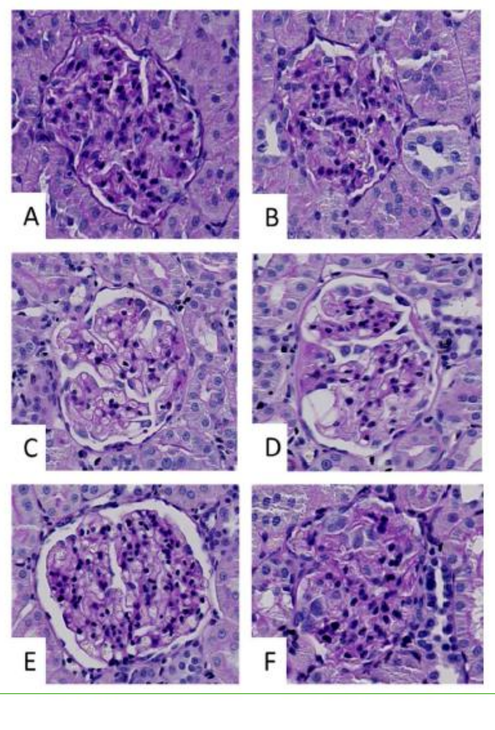
Representative images of HE staining



PAN-induced glomerular damages

Compared to untreated rats **(A;** Group 1**)**, PAN (Group 2) induced:
+ **B:** Focal mesangial cell hypercellularity (circle) with the presence of large and pale cells (arrows);
+ **C:** Thickening of the Bowman's capsule (arrow) accompanied by glomerular hypercellularity and parietal epithelial hypertrophy/hyperplasia (bracket)
+ **D:** Slight increase in mesangial matrix without mesangial cell increase.

Representative images of HE staining



Effect of XG-102 (*i.v.*)

Compared to vehicle treated animals **(A;** Group 2), XG-102 treatment induced:
+ No significant effect at 1 mg/kg (**B;** Group 3):
+ A decrease of glomerular damages including both matrix deposition and mesangial hypercellularity (**C-D**; Group 4, **E**; Group 5 and **F**; Group 6) at the doses of 2 and 4 mg/kg, respectively.

Conclusions

The glomerular morphologic and fibrotic changes seen in PAN rats are similar to those observed in human minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS; 4). XG-102 significantly reduced PAN-induced glomerular damages and the beneficial effect of curative treatment is more important than the preventive one. These results suggest that JNK inhibition should represent a good clinical strategy for the treatment of focal segmental glomerulosclerosis in humans.

References

1) Nakajima T et al., J Saitama Med Univ, 37:1-10, 2010
2) Hewitson TD et al., Methods Mol Biol, 466:41-57, 1984
3) Kanellis J et al, Nephrol Dial Transplant, 25:2898-908, 2010
4) Pippin JW et al., Am J Physiol Renal Physiol, 296:213-29, 2008

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