Megalin and Sodium-Hydrogen Exchanger (NHE)3 modulation participate to the beneficial effect of JNJ39758979 in diabetic nephropathy

1)Rosa AC. 2)Pini A. 3)Grange C. 4)Catarinicchia S. 5)Argenziano M. 6)Camussi G. 7)Chazot PL. 8)Thurmond R.

Dept. di Scienza e Tecnologia del Farmaco, Università di Tor

Diabetic nephropathy is one of major clinical and public health challenges. The paucity of effective therapy makes the identification of new therapeutic strategies a priority. In the last years, the work by our group allows to point out to the H4R as a promising pharmacological target within this context.

Aim of this study was to evaluate the contribution of Megalin and Sodium-Hydrogen Exchanger (NHE)3, two proteins expressed by the proximal tubule and involved in reabsorption processes, in the beneficial effect of JNJ39758979 in diabetic nephropathy.

Hyperglycaemia was induced in DBA/2J 7-8 week-old male mice by multiple low-dose of streptozotocyn (STZ). JNJ39758979 (25, 50, 100 mg/kg/day p.o.; 10 animals/group) was administered for 15 weeks starting from diabetes onset. Functional parameters were monitored throughout the experimental period. Biochemical and morphological analysis were performed on kidney tissue at the end of the experiment.

JNJ39758979 did not significantly affect glycaemic status or body weight. Urine analysis suggested a dose-dependent inhibitory effect of JNJ39758979 on 24 h urine volume, pH urine acidification, Albumin-Creatinine-Ratio and the Creatinine Clearance ($P<0,05$). These beneficial effects paralleled comparable effect on renal morphological integrity. JNJ39758979 demonstrated to prevent the down regulation of LRP-2, gene encoding for megalin, expression induced by STZ. The effect on gene expression is consistent with the protein expression at apical domain of epithelial tubular cells. Moreover, JNJ39758979 at both 50 and 100 mg/kg was able to contract the upregulation of NHE3 observed in diabetic mice.

In conclusion, our data suggest that JNJ39758979 exerts a direct effect on tubular reabsorption thus preserving renal function and tissue architecture.